Promotor

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GARGOYLISM

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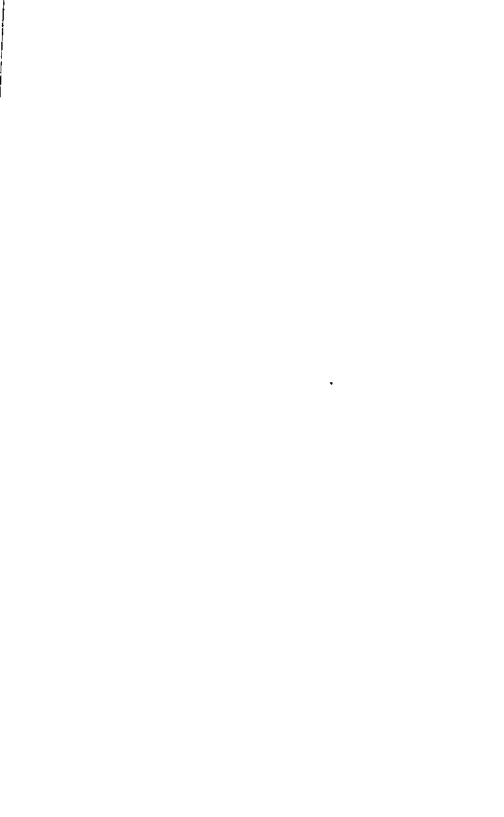
geboren te Kerkdriel

ALBERTS DRUKKERIJEN SITTARD

Aan de nagedachtenis van myn Moeder
aan myn Vader
aan Wies en de kinderen

CONTENTS

CONTENTS



Chapter I

BRIEF SYNOPSIS OF THE LITERATURE

THE FIRST APPEARANCE OF THE SYNDROME IN THE LITERATURE

In 1917 HUNTER[2] demonstrated "A Rare Disease in Two Brothers" and in 1919 HURLER[3] (from the Clinic of Pfaundler) published "Über einen Typ multipler Abartungen, vorwiegend am Skelettsystem"; both appeared independently from each other and were considered to be the first studies on gargoylism. Later it appeared that medical attention had previously been drawn to these patients (THOMPSON in 1900 and BERKHAN in 1907)[1, 58, 247]

NOMENCLATURE

HUSLER (1923) uses the name "Dysostosis Multiplex mit Schwachsinn, Typus Hurler"[16]

ELLIS, SHELDON and CAPON (1936) on account of the large head, the grotesque inhuman facial expression and the deformed extremities — to quote these authors — detected a similarity to the gargoyles of the Gothic Cathedrals. They give preference to a descriptive name, owing to the fact that the aetiology of the disease was still uncertain and thus chose the name of gargoylism[29]

One of the objections brought forward against the use of this name was that the demonic and intelligent qualities characteristic of the gargoyle are precisely those which are lacking in the facial expression of the patient with gargoylism[247]

The name of lipochondrodystrophy — originating from WASHINGTON (Brenneman's Practice of Pediatrics) — went more or less out of use when the correctness of the conceptions which formed the basis of this name was doubted[37] The syndrome has been described under many names; the name of gargoylism occurs most frequently.

The following synonyms have been used:

Hurler's (and or Hunter's and/or Pfaundler's) syndrome.

For a correct idea of what in the literature is to be understood by "Spat-Hurler" type, the main points of similarity and difference between gargoylism and Morquio's disease should now be pointed out. In both diseases an osteo-ligamentary syndrome occurs, which is to a very large extent similar although usually differing in detail. For instance, in gargoylism there are ligamentary *contractures* (manifested among other signs, by claw-hands), whereas, on the contrary, in Morquio's disease the ligaments are merely *flabby*

In both diseases there are signs of osteochondrodystrophy, which results in prominent changes on X-ray. In gargoylism these are mainly meta-epiphysial, whereas in Morquio's disease the changes are localised more epi-metaphysially. In gargoylism these changes predominate in the upper extremities; in Morquio's disease, to the contrary, in the lower ones.

Generally Morquio's disease can be differentiated from gargoylism by means of the particular differences in the osteoligamentary syndrome. This is not always the case for repeatedly transitional forms are observed in which certain particulars of the osteoligamentary syndrome show a resemblance to that of Morquio's disease, and others to that of gargoylism. To-day, therefore, it is assumed that it is not possible to establish, with certainty, the differential diagnosis between the two clinical pictures on the osteoligamentary syndrome alone. There is, however, a point of difference by means of which it is indeed possible to establish the differential diagnosis, namely: the occurrence of storage phenomena in gargoylism and their absence in Morquio's disease (including, amongst others, enlargement of liver and spleen and corneal cloudings) Moreover, in Morquio's disease the facial expression that is typical of gargoylism, is absent (the so-called "Hurler-face").

In the literature included under the "Spat-Hurler" form of gargoylism are those clinical pictures, in which on initial examination, exclusively signs of a Morquio-like osteoligamentary syndrome are observed (the "Hurler-face" and storage phenomena being completely lacking), on which the diagnosis of Morquio's disease ought to be based, whereas later on (usually not until the 20th-40th year of life), signs of accumulation become manifest (especially corneal cloudings) on account of which the diagnosis established can no longer be maintained and must be changed in gargoylism

C *The "Hurler" type and the "Hunter" type*

McKUSICK[234] differentiates between a Hurler and a Hunter type, according to the presence or absence of corneal cloudings in the patient. (Contrary to HURLER, corneal cloudings were not found by HUNTER). Various investigators consider the presence or absence of corneal cloudings due to a difference in inheritance

D *The abortive types*

By these are meant those cases of gargoylism that deviate from the classical clinical picture by presenting slighter signs, so that in isolated cases they

Polydystrophy of the Hurler (and/or Hunter, and/or Pfaundler) type.
Chondroosteodystrophy of the Hurler (and/or Hunter, and/or Pfaundler) type.
Dysostotic idiocy.

DUTCH PUBLICATIONS

In the literature on gargoylism the numerous publications of C. de LANGE occupy a special place [15, 80, 81, 92]. She also published in collaboration with WOLTRING [34] and GERLINGS, de KLEYN and LETTINGA [104].
Other Dutch publications on the same subject are those of MURK JANSSEN [17], ten BOKKEL HUININK [31], H. D. BOUMAN [35], JACOBI and WAARDENBURG [60], van WESTRIENEN [66], ROCHAT [82, 83], ZEEMAN [86], BROUWER-FROMMANN [114], WAARDENBURG [61, 118], van CREVELD [226], EDGAR [264, 265] and JELGERSMA [344].
BROEKEMA published a case of Morquio's disease [48].
The patients described by BEEBE and FORMEL, and one of the patients described by JERVIS, were of Dutch descent [157, 238].

OCCURRENCE

The disease is not a rarity. This appears from a publication by LAMY et al [308], who in 1957 carried out statistics on 269 patients. At least 30 post mortem reports have been published [274] The disease is not limited to any race [123]. Two-thirds of the number of patients examined are males [123, 308]. The age varied between 4½ months [128] and 47 years [41].

HEREDITY

The literature bearing on the genetic aspects of the disease will be discussed in chapter III.

CLINICAL VARIATIONS

A. *The typus E*

De LANGE and WOLTRING [34] called two cases "The Typus E", because — some signs being absent — they ware at first uncertain as to the diagnosis When, however, the diagnosis of gargoylism had been established beyond doubt as the result of post-mortem findings, the differentiation of this type was no longer made [34, 104].

B. *The "Spat-Hurler" type*

The "Spat-Hurler" type was distinguished by ULLRICH [97] because in this type, signs appear from which the diagnosis of gargoylism may be made later than is usually the case in gargoylism (as late as the 2nd, 3rd or 4th decade), while in the period prior to the appearance of these symptoms, the clinical picture is similar to that of Morquio's disease.

there is an umbilical hernia and a diastasis of the right abdominal muscles. The scrotum may be oedematous. On the skin of the lower legs changes may occur resembling livedo racemosum Furthermore, acrocyanosis has been described The nails are often deformed. The hands are short and broad and the fingers crooked. The little finger is bent radially. In the feet analogous changes may be observed although in a lesser degree The cheeks are usually a vivid red The hair on the head — which generally gives a bristly impression — is irregularly spread. The eyebrows are joined over a broad and flat or sunken nasal bridge. The forehead is arched. Moustache-growth may also be observed The lips, tongue and gums are coarse and thick; the teeth small and widely spaced. The tonsils are large. The ears are coarse and the lobes especially large.

Examination of the back may reveal a scoliosis, kyphosis or kyphoscoliosis at the junction of the thoracic and lumbar vertebrae or a lumbar hypolordosis. The posture is stiff. In standing, it is remarkable that the upper legs are held in a flexed position; movements are marked by a lack of suppleness. In most joints movement is limited on account of ligamentary contractures The most striking of these are the tendo contractures of the fingers (mainly at the second interphalangial joint) and the tendon contracture of the upper legs. Movement of the spinal column appears also to be limited, as well as the expansion of the thorax on inspiration[274].

Respiration is accompanied, to a greater or lesser degree by a sterrorous sound. Physical examination may reveal signs of cardiovascular disturbance[2, 49, 229, 331]. Very often there is a chronic bronchitis The liver is frequently enlarged and the spleen also, although this is less often. Enlargement of the lymph glands may occur Oedema is rare. Gastro-intestinal disturbances are generally absent. In many cases the impression is given that audition decreases progressively; deafness may also occur. It is not surprising that data on aural function, timing fork tests and audiometric examination are scarce in the literature, when one remembers that as a rule the patients cannot render the co-operation required for these tests, owing to their limited intellectual powers[49, 87, 104]. Data on the caloric irritability of the labyrinth are likewise scarce[97, 107, 156, 227]. ULLRICH points out that the labyrinth functions are generally described as being normal[97]. DUHAMEL[107] and FONTAN et al[156] found the labyrinth irritability abolished, while TURPIN and LAFOURCADE[227] established normal labyrinth reactions in their patients

In 70.9% of the cases corneal cloudings are found[166]. In cases that are negative on using a magnifying glass, slit lamp examination is necessary in order to exclude the condition with certainty[147]. Should there be corneal cloudings, examination of the fundus may be difficult if not impossible, so that an existing optic atrophy may escape diagnosis.

The cloudings as such are usually not accompanied by blindness, in the latter cases there is generally an optic atrophy Incidentally the eye examina-

cannot or hardly ever be diagnosed as gargoylism. With the help of hereditary data it is ultimately possible to arrive at the diagnosis of "forme fruste" of gargoylism. Some publications have been dedicated to the symptomatology of the "formes frustes"[157, 171, 174, 200].

E. *The typus Amstelodamensis*

The typus Amstelodamensis, introduced by C. de LANGE[15] as a type of gargoylism, offers few perspectives for the study of a possible connection with gargoylism, owing to the lack of post mortem findings and its extreme rarity.

THE CLINICAL PICTURE

According to a statistical survey by A. GIAMPALMO and V. GIAMPALMO[112] the signs most frequently occurring are corneal cloudings, enlargement of the liver, spleen, skeletal changes and psychic disturbances With the exception of the skeletal changes, — which, once developed, remain well-nigh constant — the changes are of a progressive nature. It often appears that the birth was difficult (breech presentation or forceps delivery) which gives rise to the supposition that the skull was already deformed at birth. As a rule the case histories mention the frequent occurrence of infections of the respiratory tracts.
It is striking that when gargoylism is diagnosed the early signs are generally observed during the first decade According to whether the first appear before or after the third year of life, referance is sometimes made to an "early", or "late" form of the disease in the literature. Completely independent of this is that clinical form of gargoylism referred to in the literature as the "Spat-Hurler" type, as we mentioned before.
The patient's general appearance may alone yield important data for the arriving at a diagnosis
The disharmonious dwarfism with the large head which seems to rest on the trunk and especially the gargoylic facial expression give a particular aspect to the appearance, at once raising in those familiar with the picture, suspicion as to the correct diagnosis. The dwarfism is not an obligatory symptom An above normal body height, however, is only very rarely described[19].
Owing to the deposition of fat in the gluteal region, the fat protruding abdomen, the wide thorax and the large head, the extremities, and especially their distal parts, sometimes appear hypoplastic
Hypertrichosis occurs in 30% of the patients[112]
The excessive growth of hair affects particularly the back and the extensor sides of the limbs. The skin is generally thickened and its elasticity lessened[240].
In some cases nodules were observed between the scapula and the axillary line[204, 235], or changes in pigmentation resembling a disseminated melanosis[305]. Also vitiligo[128] and "mongolian spots"[179] may be present. Very often

mentioned[23, 106, 111, 178, 223, 227, 266]. Rarely the following symptoms are described: athetosis[61], abundant flow of saliva[61], lessening of pain-sense[153], ataxia[267], bilateral spastic pyramidal syndrome[153, 186, 243], nystagmus[227], convulsions[135, 227] and hyperthermia of a diencephalic origin[153].
Important observations in the field of gargoylism were made by JERVIS[157]. At the examination of a patient at the age of five, he found no neurologic changes. The pneumoencephalogram was normal. At the age of six there was a mild spastic paresis of the legs and bilaterally a Babinski sign. Since then the hypertonia not only increased in the legs, but also extended to the arms. At the post mortem of the patient aged eleven years a slight ventricular dilatation was found.
Electroencephalographic examination has repeatedly been described[103, 117, 127, 143, 157, 159, 192, 216, 227, 233, 239, 267, 288, 314]. Generally, diffuse, slow dysrhythmias are recorded, sometimes of an abnormally high voltage[157, 239].
The vertebral anomalies frequently occurring in the thoracolumbar region seem seldom accompanied by symptoms of a transverse lesion or of a peripheral nervous affection. That a partial obstruction of the spinal canal may exist was proved by McKUSICK by means of myelography[274].
The musculature of the legs may be hypotrophic and the periost reflexes sometimes lowered. Strong atrophies, fasciculär contractions and hypotonia are not found as a rule. Electromyographic examinations are not mentioned in the literature.

X RAY EXAMINATION

X-ray examination generally reveals numerous changes. The most important of these are the following:

Skull

The fontanel closing is often delayed. The skull circumference is nearly always too large; the skull may be relatively high, long or broad. Microcephaly is only seldom observed[175, 260]. The frontal bone is prominent. The wall of the skull may be either thick, normal or thin. In cases of marked hydrocephalus, a thin calvarium is often observed. In the region of the skull sutures, the bone may be thickened. The body of the sphenoid is generally too high, and the distance from the ala magna to the base of the nose decreased. Hypertelorism is a frequently occurring symptom. The pneumatisation of the mastoid bone is *generally* qualified as poor. The sella turcica may be normal, but it can also be *enlarged* (*in a* balloon- or shoe-shaped form). The jaws are strongly developed and the angle of the lower jaw may be too obtuse.

Thorax

The clavicles are too massive, especially as far as the sternal part is concerned. The thorax is broad and *the ribs*, which are thickened, run in an undulating and horizontal manner. On the level *of the* attachment to the sternum and the vertebrae the lower ribs are narrowed like a thin *paint brush*.

tion may reveal varied changes. The most frequent among these are — apart from corneal cloudings — megalocornea (generally without increased intra-ocular increase of tension) and optic atrophy. Moreover a retarded reaction to mydriatics is repeatedly found [31, 60, 74]. For a full survey on ocular changes occurring in gargoylism reference is made to the literature on the subject concerned [61, 74, 90, 180, 199, 208, 221, 224, 261, 269, 294, 311, 337].

Psychic disturbances occur, according to A. GIAMPALMO and V. GIAMPALMO [172], in 74.5% of the number of cases observed. The seriousness of the psychic disturbances depends, according to LIESSENS, on the rate at which the morbid process develops, and on the time at which the first symptoms manifest themselves [243, 273]. The earlier they appear the more serious the psychic symptoms. There are, however, exceptions to this rule. The "early" cases are generally characterized by a retarded psychomotor development. These patients learn to walk late and the development of speech is very deficient. They are conspicuous for their anxious disposition and negativistic attitude. Their behaviour necessitates constant supervision. Grave types of oligophrenia are not rare, while in the long run psychic deterioration eventually manifests itself [273].

In the "late" cases (the first signs appearing after the age of three years) clear psychic disturbances may be absent. Usually, however, psychomotor development is normal at first, later on however progressive deterioration takes place. It is difficult to decide exactly in how far the sensory disturbances play a part therein [273] Regarding the specificity of the psychic disturbances LIESSENS states "Le deficit intellectuel et psychique ne présente aucun type particulier, ni aucun caractère spécifique" [273].

In a small number of cases the psychic functions are and remain normal. The examiner may be severely hampered by the psychic disturbances, characteristic of these patients. The children may ward off his hand. Palpation and reflex examination are not simple under such circumstances. One often fails to coax the patient into co-operating Incontinence is usually present Eventually most patients become bed-ridden. Generally, owing to increasing disturbance in behaviour, admission to an institution becomes necessary at an earlier stage.

Symmetrical generalized dilatation of the cerebral-ventricles and hydrocephalus are the most outstanding changes found on *neurological examination* In the publications by HUNTER and HURLER these changes are not mentioned by name, but at the post mortem of one of HURLER's patients, a hydrocephalus was found [18].

DAVIS and CURRIER [23] and ever since, many other investigators [28, 41, 132, 156, 157, 227, 263, 267, 298], found dilatation of the ventricles by means of pneumoencephalography. Cortical atrophy may occur [132, 265] The existence of a hydrocephalus may be indicated by a too large and still increasing circumference of the skull, a rarefaction of the skull-vault and a cracked pot sound. Optic atrophy and pigmentary anomalies in the fundus are seldom

of alpha 2 globulins is often increased Sometimes there is hypochromic anaemia Cupremia may be present[251] as also hypermucoproteinemia[251]. The lipoproteins in the blood serum may show qualitative and quantitative changes[278, 309], and the neuraminic acid content of the blood serum may be increased[280].

The blood sugar curve is within normal limits Marked and constant changes in the calcium, phosporus and phosphatase values are absent. The cholesterol content is sometimes markedly increased. The liver function tests are nearly always normal. Routine urine tests reveal few peculiarities.

DORFMAN and LORINCZ[303] and MEYER et al[327] proved that in the urine of gargoyle patients a mixture of mucopolysaccharides was present, which according to MEYER et al consists mainly of chondroitine-sulphuric acid B (Ch S-B) and heparitin sulphuric acid

Incidentally changes were found in the hormonal excretion BINDSCHEDLER and co-workers[43] found decreased secretion of adenohypophysary hormones in the urine (2 cases). SARTORI[187] found a normal excretion of 17 ketosteroids in the urine, together with an increased excretion of 11 oxycorticosteroids RODECK[206] also found a normal excretion of 17 ketosteroids GUELI and SEVERI[223] by means of Thorn's test found normal values. In paperchromatographic tests of the urine, changes were sometimes found[245] (pathologic aminoaciduria). The basal metabolic rate may be either normal, decreased or increased

GILLILAND[185] found a normal excretion of radioactive iodine I[133]. Routine studies of the spinal fluid, Pandy, Nonne, cells, protein content and colloidal curves afford no peculiarities

PATHOLOGICAL ANATOMY

Prominent is the "gargoyle" cell change[274]. This gargoyle cell change is characterised by swelling, enlargement, vacuolisation of the cytoplasma (creating a foamy appearance) and aso by eccentric position of the nuclei The cells give the impression of [illegible] change. Besides cellular changes, extracellular ones may be observed, e g in the form of proliferation of collagen fibres and increase of the basal substance[131].

For a complete survey of the changes found in gargoylism, we refer to publications relating to this matter[123, 131, 201, 274]. Only the most important data are now enumerated

Liver

This organ is often considerably enlarged The liver cells, and sometimes also the Kupffer cells, then show the typical gargoyle cell change.

Spinal column

The centre of the anomalies is the thoracolumbar junction. The adjoining vertebrae may have changed in a similar though generally less spectacular way. There may be an arcuate kyphosis, possibly kyphoscoliosis or a spondylolisthesis. The lumbar lordosis is generally flattened. The bodies of the twelfth thoracic and the first lumbar vertebrae are often too small, while the frontal top quarter is wholly or partially invisible in X-ray films ("fishhook" shape). Sometimes these changes occur combined with those especially typical for Morquio's disease (generalised platyspondylia and tongue-shaped projections on the front of the vertebral body).

Hands

Generally the phalanges are suppository-shaped. The phalanges and metacarpals are short and broad, and the diaphysery trabeculation is coarse. The base of the metacarpals may taper off to a point. The number of ossified nuclei carpal centres may be small in proportion to the age. On the feet analogous changes may be observed, although they are always less intensive.

Humerus and femur

The heads of humerus and femur are often flattened. The neck is too broad The epiphyses are of irregular shape. The joint socket is often shallow. Coxa valga and genua valga frequently occur.

CAFFEY[202] observed in three cases in which classical symptoms of gargoylism only appeared later, in early youth the occurrence of a serious generalised "demineralisation". CRAIG[250] did not see abnormalities on an X-ray film made a fortnight before the birth of twins (a brother and sister) Later the twins developed unmistakable symptoms of gargoylism

Extensive surveys of radiologic changes occurring in gargoylism were published, among others, by HARVEY, GUY and LERIQUE, LEFEBRE and co-workers, SEYSS, MERLEN, van den DORP and MERLEN, LACKNER and ZELLWEGER and co-workers[89, 161, 162, 163, 191, 228, 234, 307] Also the radiological differences between gargoylism and Morquio's disease generally form a point of discussion in these publications.

LABORATORY STUDIES

These afford few positive data of importance for the diagnosis An exception to this is Reilly's anomaly (abnormal granules in the leucocytes) which can be shown to be present in a number of cases[70] This abnormal granulation can be made visible by means of the Giemsa-Wright staining method[70], GRIFFITHS and FINDLAY[319] and BUHOT[330, 338] state the occurrence of "ring-shaped inclusions" in the plasma cells of the bone marrow and "granular inclusions" in the histiocytes in two cases where the anomaly of Reilly was absent. According to LÖWENTHAL[241] the percentage in the blood serum

of alpha 2 globulins is often increased Sometimes there is hypochromic anaemia. Cupremia may be present[251] as also hypermucoproteinemia[251]. The lipoproteins in the blood serum may show qualitative and quantitative changes[278, 309], and the neuraminic acid content of the blood serum may be increased[280].

The blood sugar curve is within normal limits. Marked and constant changes in the calcium, phosporus and phosphatase values are absent. The cholesterol content is sometimes markedly increased. The liver function tests are nearly always normal. Routine urine tests reveal few peculiarities

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PATHOLOGICAL ANATOMY

Prominent is the "gargoyle" cell change[274]. This gargoyle cell change is characterised by swelling, enlargement, vacuolisation of the cytoplasma (creating a foamy appearance) and aso by eccentric position of the nuclei The cells give the impression of being "inflated". Especially the liver parenchyma cell is affected by this gargoyle change, but in principle any organ or tissue may contain cells that have undergone such a change. Besides cellular changes, extracellular ones may be observed, e g in the form of proliferation of collagen fibres and increase of the basal substance[131].

For a complete survey of the changes found in gargoylism, we refer to publications relating to this matter[123, 131, 201, 274]. Only the most important data are now enumerated.

Liver

This organ is often considerably enlarged. The liver cells, and sometimes also the Kupffer cells, then show the typical gargoyle cell change.

Spleen

The spleen is also often enlarged, although in a lesser degree than the liver. At histological examination the reticuloendothelial cells surrounding the sinuses may prove to be considerably enlarged, and many enlarged mononuclear cells may be found in the spaces among the sinuses [201].

Kidney

Here also gargoyle cell changes are sometimes found. Then the tubular cells are mostly affected [79].

Heart and blood vessels

According to EMANUEL [229], in 77.7% of the number of post mortems, cardiac changes are found. The valves may be thickened and contain large vacuolised cells. Besides calcification, chondroid changes may be found [106]. In the cardiac muscle vacuolated cells are sometimes found [39, 131]. The blood vessels, among which the coronary artery, may show similar changes, causing the lumen to be narrowed. A survey and a detailed description of the cardiovascular sclerosis, sometimes found, is given by COTTIER [292].

Lungs

The lung parenchyma frequently shows numerous vacuolated macrophages lining the alveolar walls [29, 39, 123, 133, 186, 253, 339] and occasionally a thickening of the alveolar membrane is found [39]

Trachea

Sometimes pathological processes are seen involving the cartilage and perichondrial tissues of the trachea [104, 133].

Eyes

In the cornea, Bowman's membrane may be replaced in many places by large, vacuolised cells. In the interlamellar spaces granular matter may be found. The ganglion cells of the retina may show gargoyle cell changes [35, 225, 269]. In the sclera gargoyle cells may be found [180]

Skin

The cutis may be thickened owing to thickening of the collagen fibres which are irregularly arranged [195, 204, 240].

Thymus gland

This organ is sometimes enlarged [25, 138, 288].

Ears

Histological examinations mention the occurrence of stenosis of the auditory canal [88], ankylosis of the joints between the tympanic bones [88, 227], atrophy of Corti's organ [104], small crystae ampullares [104], irregular lumen of the

semicircular canals[85], and degenerative or thesaurismotic changes in the cells of the cochlear and vestibular ganglions[86, 271].

Reticuloendothelial system

Histopathological changes of the reticuloendothelial system are often found, marked by proliferation and gargoyle cell change in the elements belonging to this system[201].

Pituitary gland

When at a post mortem an enlarged pituitary gland is found, it is generally the anterior part that is seen to be enlarged and especially the chromophobic cells, besides increase, show abnormal vacuolation[39, 79, 81, 113, 184, 259, 263, 294].

Skeleton, cartilage and joints

SCHMIDT[67], de LANGE et al[104], HIENZ[210, 345] and NISBET and CUPIT[267] have found disturbances of the enchondral ossification. The cartilage cells may show gargoyle changes. The ligaments and periarticular tissues may show thickening and gelatinous changes.

GIROL and BENEDETTI have found diaphysial changes in one case as a result of massive infiltration of foam cells in the bone marrow[321].

Sternal puncture and blood

In a number of cases REILLY[76] proved by Giemsa-Wright's staining method the presence of large dark lilac coloured granules in the leucocytes (especially the polynuclear ones) of the peripheral blood and also in the sternal punctate fluid. Similar granules were found by BUHOT[330] in the plasma cells and histiocytes of the bone marrow, while GRIFFITHS and FINDLAY[319] mention the occurrence of "ring-shaped inclusions" in the plasma cells of the bone marrow.

The nervous system

The first organ of which histological examination is mentioned in the literature, concerns the cerebrum of one of the patients, described by HURLER[10, 16, 18], in which dilatation of the lateral ventricles was found. From the post mortem reports it appears that hydrocephalus or a slight dilatation of the lateral ventricles occurs frequently. There is sometimes local atrophy of the cerebral cortex. Besides, it may also occur that the sulci are straight by broadening of the gyri[79].

The leptomeninges are often thickened[158, 180, 247].

As a consequence of the meningeal changes and the hydrocephalus, the optic nerves may have a pronounced abnormal course[79].

On microscopical examination, the changes in the nerve cells come to the fore, which are morphologically difficult to distinguish from the changes of the ganglion cells in Tay Sachs, Stock-Spielmeyer-Vogt's, Niemann-Pick's and Gaucher's diseases. These are characterised by considerable enlargement of the cell and eccentric nuclear position. The neurofibrils often lie on the periphery

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Ears

Histological examinations mention the occurrence of stenosis of the auditory canal [88], ankylosis of the joints between the tympanic bones [85, 227], atrophy of Corti's organ [104], small crystae ampullares [104], irregular lumen of the

semicircular canals[88], and degenerative or thesaurismotic changes in the cells of the cochlear and vestibular ganglions[88, 271].

Reticuloendothelial system

Histopathological changes of the reticuloendothelial system are often found, marked by proliferation and gargoyle cell change in the elements belonging to this system[201].

Pituitary gland

When at a post mortem an enlarged pituitary gland is found, it is generally the anterior part that is seen to be enlarged and especially the chromophobic cells, besides increase, show abnormal vacuolation[39, 79, 81, 113, 184, 259, 261, 284].

Skeleton, cartilage and joints

SCHMIDT[87], de LANGE et al[104], HIENZ[210, 345] and NISBET and CUPIT[247] have found disturbances of the enchondral ossification. The cartilage cells may show gargoyle changes The ligaments and periarticular tissues may show thickening and *gelatinous changes.*

GIROL and BENEDETTI have found diaphysial changes in one case as a result of massive infiltration of foam cells in the bone marrow[321].

Sternal puncture and blood

In a number of cases REILLY[70] proved by Giemsa-Wright's staining method the presence of large dark lilac coloured granules in the leucocytes (especially the polynuclear ones) of the peripheral blood and also in the sternal punctate fluid. Similar granules were found by BUHOT[330] in the plasma cells and histiocytes of the bone marrow, while GRIFFITHS and FINDLAY[119] mention the occurrence of "ring-shaped inclusions" in the plasma cells of the bone marrow

The nervous system

The first organ of which histological examination is mentioned in the literature, concerns the cerebrum of one of the patients, described by HURLER[10, 16, 31], in which dilatation of the lateral ventricles was found From the post mortem reports it appears that hydrocephalus or a slight dilatation of the lateral ventricles occurs frequently. There is sometimes local atrophy of the cerebral cortex Besides, it may also occur that the sulci are straight by broadening of the gyri[79]

The leptomeninges are often thickened[158, 180, 247]

As a consequence of the meningeal changes and the hydrocephalus, the optic nerves may have a pronounced abnormal course[79].

On microscopical examination, the changes in the nerve cells come to the fore, which are morphologically difficult to distinguish from the changes of the ganglion cells in Tay Sachs, Stock-Spielmeyer-Vogt's, Niemann-Pick's and Gaucher's diseases These are characterised by considerable enlargement of the cell and eccentric nuclear position The neurofibrils often lie on the periphery

and Nissl's bodies are reduced or have disappeared. The cytoplasma usually has a granulated aspect, and sometimes small vacuoles are observed The number of nerve cells is generally not notably reduced. Demyelinisation and gliaproliferation are not prominent features[81, 266, 315]. Within a certain formation *(layer or nuclear region) the degree of cellular change is more or less* equal, but among the various formations there may be considerable differences in this respect[266]. Especially in the brainstem important contrasts may occur.

Why the cells in certain formations are not or hardly, and in others greatly changed, might be linked up with certain morphological cell characteristics[266]. According to some authors, the big cells in the nucleus caudatus and the putamen are changed in a large measure, whereas in the small ones hardly any morphological changes can be observed[266, 315]. The perivascular spaces may be broadened (especially in the white matter) and the vascular endothelium proliferated[18, 127, 133, 186, 217]. The dendritic processes of the cells of Purkinje may be swollen in an oval manner[157, 284]. In the spinal cord it is especially the anterior horn cells that show changes similar to the ganglion cell changes in the cerebrum. In the spinal cord the enlargement of the cells is even more pronounced than in the cerebrum Also the ganglion cells of the peripheral and autonomic nervous system may show changes analogous to those of the cerebrum.

Adrenals, gonads, thyroid gland

Sporadically, in the parenchymatous cells of these organs, gargoyle cell changes are found.

Pancreas

Only seldom typical cell changes have been observed In a case, described by NJÅ[112], the pancreas was stated to be degenerated diffusely

THE CHEMICAL NATURE OF THE ACCUMULATED SUBSTANCE

A *In the nerve cells*

All investigators with the exception of BISHTON et al[284] find an increase of hexosamine and or neuraminic acid in the cerebral cortex[116, 169, 264, 301] and on the strength of these findings (because neuraminic acid and hexosamine are components of gangliosides) they assume a surplus of gangliosides. This glycolipid is supposed to be mainly localised in the nerve cells[169] According to DIEZEL and SEITELBERGER the substances accumulated in the nerve cells are difficult to dissolve[299, 301], as a result of their combinations with proteins So far, it has not been proved that the chemical composition of the accumulated gangliosides is markedly different from those occurring normally in the cells — as was shown for the first time by KLENK.

BRANTE considers only the *excess* of gangliosides in the nerve cells to be

pathological and not the *nature* of the gangliosides themselves[298]. Of the chemical staining methods applied, especially the P.A.S. and Sudan stains, and the Nile blue sulphate method are often positive[169, 253, 262, 284, 299, 315].

B. *In the visceral organs*

What substances are accumulated in the gargoyle cells of the liver, spleen and other organs?

At first it was thought to be lipids, but the quantities shown by staining were generally not in accordance with the measure of cell enlargement. Sometimes no lipid could be demonstrated[104].

C. de LANGE[9], STRAUSS c.s.[123] and HENDERSON c.s[201] found no increase of the lipid percentage in the liver. Neither did the glycogen percentage of the liver appear to be markedly altered. BRANTE[209] considers the cause of the difficulties in respect of identification of the accumulated substance to be the dissolving of the vacuolar content in the fluids generally used for fixation.

In connection with this, the use of special fixation fluids (e.g. lead acetate or glacial acetic acid)[209, 298] is recommended. Besides BRANTE other investigators have also succeeded in staining the vacuoles in this manner[247, 262, 298, 340]. BRANTE showed an excess of mucopolysaccharides. Moreover, the gargoyle cells contain neutral fats only in insignificant quantities, and also much glycogen, the percentage of which does not seem sufficient to call it unphysiological. Sometimes too, ganglioside-like substances could be proved to be present in the gargoyle cells of different organs. Apart from the above mentioned surplus of mucopolysaccharides, the strong solubility must be considered abnormal, as well as the fact that they are mostly found intracellularly[298].

SEITELBERGER[272, 301], contrary to BRANTE, is of opinion that the *mucopolysaccharides* do not occur in a free form, but are chemically combined to lipids, and he therefore speaks of accumulation of glycolipids. DIEZEL, GUELI and SEVERI[205, 299] are of opinion that the accumulation products may differ from case to case.

UZMAN arrives at the conclusion that in the accumulation product two substances of *different chemical* composition are present, a complex polysaccharide and a glycolipid[257].

STACEY and BARKER[276] and MEYER et al[327] conclude that a heparin-like substance is present which normally is not found.

THE CAUSE, NATURE AND ORIGIN OF THE DISEASE AS WELL AS THE ORIGINATION OF ITS SYMPTOMS

A. *The cause of the disease*

In studying the literature it is quite clear that the cause of the disease is definitely not known. More and more investigators are of opinion that in the

and Nissl's bodies are reduced or have disappeared. The cytoplasma usually has a granulated aspect, and sometimes small vacuoles are observed. The number of nerve cells is generally not notably reduced. Demyelinisation and gliaproliferation are not prominent features[81, 266, 315]. Within a certain formation (layer or nuclear region) the degree of cellular change is more or less equal, but among the various formations there may be considerable differences in this respect[266]. Especially in the brainstem important contrasts may occur.

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leads to disturbances in the supporting tissues and secondly to *accumulation* of mucopolysaccharides in the organs.

1954 WIEDEMANN[249]: disturbance in the reach of proteincarbohydrates metabolism.

1955 UZMAN[257]: a *genetic determined* defect of the structural polysaccharides.

1955 SEITELBERGER[272], default of the inter-cellular glycolipid metabolism.

1957 BRANTE[258]: it is possible that primarily the protein metabolism is disturbed and subsequently the binding process between the proteins and the mucopolysaccharides proceeds in an abnormal manner.

1958 MEYER, GRUMBACH, LINKER, HOFFMAN[327]: *gargoylism* represents an overproduction of certain mucopolysaccharides due to a genetically determined error of differentiation of fibroblasts

From this enumeration it can be *seen* that by *far the greatest number* of the investigators are in agreement that in the nosological system gargoylism should be classified among the metabolic diseases, while with regard to the question what chemical substances are involved in this metabolic disturbance no unanimity exists

At first it was assumed that the disease would be the expression of an abnormal course of the fat metabolism[30]. This opinion has been reconsidered and now the disease is rather seen as the expression of an abnormal course of the metabolic processes in the reach of the mucopolysaccharides[258, 257, 327] glycolipids[272], or of the carbohydrates and/or protein metabolism[249].

Besides that, most investigators assume that the metabolic disorders are coupled with accumulation, and they are of opinion that gargoylism should be classified amond the storage reticuloses[112, 209, 327]. In this respect then, they see a resemblance with Tay-Sachs', Stock-Spielmeyer-Vogt's, Gaucher's, Niemann-Pick's diseases and the xanthomatoses osseum.

BIELSCHOWSKY[130] who made an intensive study of the pathogenesis of the storage reticuloses is of opinion that the product stored in the reticuloendothelial system and in the nerve cells is accumulated as a result of a metabolic anomaly with regard to the chemical substance that is stored.

Opposed to the opinion of BIELSCHOWSKY is that of SCHAFFER[170], who assumes that the storage is not the result of an excess of a certain chemical substance, but that it should be *seen as a metabolic* error *affecting* the protoplasma of that particular cell system, the cause of which is still unknown. In the light of this opinion, the substances accumulating in abnormal quantities within the cells need not be taken as emanating from an excess in the blood, but they appear as the manifestation of a disturbed cell metabolism, so that it is a question of *phanerosis*. In the literature on gargoylism we encounter these fundamentally different views on the *origin* of *the accumulation*

origin of the disease, disturbances in certain enzymes must be regarded as an important conditional factor. The view of ERNOULD[137] that *disturbance* of the thyreotropic hormone of the pituitary gland is of great significance was not shared by other investigators, because the existence of this deviation could actually not be proved.

A very striking factor is the heredity. That gargoylism is a hereditary disease is now generally accepted. This means that in one or both parents or in their ascendants, a pathological gene change has taken place which is a conditional factor for the origin of gargoylism. This change might, according to certain authors, *come about by abortifacients or by alcoholism*[173]. *The genetic aspects* are to be elucidated in chapter III.

B. *Nature and aetiology of the disease*

The opinions on the aetiology has repeatedly been altered. We chronologically quote some of them

1917 PARKES-WEBER[2] (discussion after demonstration by Hunter): endocrine disturbance.

1917 BLUNDELL-BANHART[2] (discussion after demonstration by Hunter). multiple congenital developmental errors

1917 HURLER[3]: developmental errors combined with degenerative characteristics and endocrine-like conditions.

1919 PFAUNDLER[4, 5]. a familiar divergence, which mainly effects the supporting tissue.

1936 ELLIS[28]: disturbance of metabolism, comparable with Gaucher's disease.

1936 COCKAYNE[30]. disturbances of lipid metabolism with accumulation in liver and spleen.

1937 ASHBY et al[32] disease resembling amaurotic idiocy.

1940 HENDERSON[58]. congenital disturbance of the lipid metabolism.

1940 HÄSSLER[63] gargoylism is the fourth lipidosis

1942 DE LANGE[92]. gargoylism must be looked upon as a lipidosis on account of the large conformity of the cerebral defects with those of Tay-Sachs and Niemann-Pick

1948 STRAUSS[131] disturbance intra-cellular metabolism The question whether gargoylism is a form of lipidosis remains to be seen.

1948 REILLY-LINDSAY[132]. hereditary constitutional metabolic disease — probably in the reach of combined carbohydrates — coupled with accumulation

1952 SMITH-HEMPELMANN-MOORE-BARR[194] dysmetabolism of a substance related to glycogen.

1952 BRANTE[209]: a dysmetabolism of mucopolysaccharides which primarily

leads to disturbances in the supporting tissues and secondly to accumulation of mucopolysaccharides in the organs.

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LINDSAY[132], HUEPER, TOLENTINO and TERRAGENA[255], conducted animal experiments in which, after intravenous injection of macromolecular carbohydrate, they saw disturbances appear which — according to these authors — showed a resemblance to those in gargoylism and concluded that the substance accumulated *in the cells emanates from an excess in the blood* MEYER et al[327] give as hypothesis that mucopolysaccharides are accumulated as a result of an over-production of these substances caused by metabolic disturbances taking place in the connective tissue. Contrary to this *opinion STRAUSS*[131], *KLENK*[272], *SEITELBERGER*[272] and *BAMATTER*[283] consider that the accumulation is a manifestation of a metabolic disorder taking place in the cells concerned.

C. *Origin of the individual symptoms*

a. *Enchondral dysostosis*

The epiphysial cartilage ossification disturbances and the dwarfism connected with them are seen by some investigators as manifestations of an endocrine dysfunctioning, by others as a primary result of metabolic disturbances localised in the connective tissue itself[39, 132, 133, 209, 237] Based on the topographic distribution of the skeletal changes, MAU considers it probable that the pathogenic action takes place at a certain stage of the embryonic development, and that the length of this influence is bound to a certain time limit[316]

b. *Umbilical and inguinal hernias, ligamentary contractures and skin changes*

The umbilical and inguinal hernias, skin changes and contractures are generally considered the result of metabolic disturbances in the connective tissue.

c. *The enlargement of liver and spleen*

The enlargement of liver and spleen are attributed to enlargement of the parenchyma cells, and sometimes to the increase of cells belonging to the reticuloendothelial system.

d *Cardiac changes*

The cardiopathy was at first considered erroneously to be a congenital development anomaly. Later on, however, cardiovascular sclerosis was found to be present in a number of cases, as the result of gargoyle metabolic disturbances[39, 122, 153, 229, 292]

e *Corneal cloudings*

The corneal cloudings are, according to most authors, caused by the presence of gargoyle cells in Bouman's membrane[315]. NEWELL and KOISTINNEN[369], however, consider it unlikely that these phenomena should in any way be connected. They are more inclined to assume that structural changes in the connective tissue of the cornea have a causal relation to the cloudings

f *Deafness*

In the literature no unanimity is reached on the explanation of the presence of deafness or impaired hearing MEYER and OKNER [49] find that they must assume otosclerosis whereas WOLFF [85] is more inclined to assume conduction deafness in this case. In her own case WOLFF observed a greatly reduced diameter of the external auditory meatus

The malleoincudal joints were found to be ankylotic. The organ of Corti was normal In the brain histological changes were absent.

De LANGE, GERLINGS, de KLEYN and LETTINGA [104] ascribe the deafness to atrophy of the organ of Corti. Here too, histological changes were absent

TURPIN, LEFEBRE, CHASSAGNE and DUCHÊNE [117] note a conduction deafness as a result of ankylosis of the auditory ossicles

RICCI and ANCETTI attribute the deafness to degenerative or thesaurismotic changes in the cells of the cochlear ganglion [271].

g *Reilly's anomaly*

The abnormal granules discovered by REILLY in the leucocytes in a number of cases were taken to be a maturating disturbance. According to BRUGSCH [148] Reilly's anomaly had previously been described by JÜRGENS, and there is much resemblance with Alder's anomaly, in which similar granules are found in the leucocytes of seemingly healthy children who afterwards developed serious osseous deformities. ALDER [160] states that all the cases observed by him were accompanied by bonegrowth disturbances, but he considered the granules not to be the result thereof. It is a maturating disturbance of the blood cells, in which a hereditary factor is of real significance LAVES [183] makes known that the granules mainly contain a polysaccharide component corresponding to a hyaluronic acid ester. After treatment with hyaluronidase the granules disappeared.

ULLRICH and WIEDEMANN [216] regard Alder's and Reilly's anomalies as identical phenomena UNDRITZ [248] also supports this idea.

GUELI and SEVERI [223] suggest the hypothesis that Reilly's anomaly is nothing but an altered stainability of the eosinophile cells.

h *Psychic disturbances.*

The organic changes in the brain must be held responsible, according to REILLY, LINDSAY and McGILLIVRAY, for the psychic disturbances [132, 191].

i. *Hydrocephalus.*

In respect of the cause of the hydrocephalus, the conception of BISHTON and co-workers [264] is the most popular one. These authors consider the thickening of the pia and arachnoid responsible for a partial or complete obstruction of the subarachnoidal space

According to these authors, in cases accompanied by leptomeningeal thickening, ventricular widening was always found [264]. STRAUSS [131] ascribes the

LINDSAY[132], HUEPER, TOLENTINO and TERRAGENA[285], conducted animal experiments in which, after intravenous injection of macromolecular carbohydrate, they saw disturbances appear which — according to these authors — showed a resemblance to those in gargoylism and concluded that the substance accumulated in the cells emanates from an excess in the blood. MEYER et al[327] give as hypothesis that mucopolysaccharides are accumulated as a result of an over-production of these substances caused by metabolic disturbances taking place in the connective tissue. Contrary to this opinion *STRAUSS*[131], *KLENK*[272], *SEITELBERGER*[272] and *BAMATTER*[289] consider that the accumulation is a manifestation of a metabolic disorder taking place in the cells concerned.

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of one disease[93, 132, 157, 167, 262]. Most authors are of opinion that there are sufficient clinical differences between gargoylism and Morquio's disease to maintain them for the time being as separate syndromes[168, 156].

PROGNOSIS AND THERAPY

The patients generally do not get older than ten to fifteen years. According to FALCHI and MIDULLA the average span of life for girls is 8 years 4 months, and for boys 11 years. A higher age may be reached. The latter holds true mainly for the abortive cases and for the cases without mental deterioration[183]. They generally die as the result of cardiopathy or — owing to decreased thoracic mobility — from an pulmonary affection[339]. A number of patients died after a seemingly harmless operation[86, 318], or as the result of an anaesthetic[104, 201].

Of the symptomatic therapy (a causal therapy has not yet been described), we mention the, in fact unimportant, improvement sometimes achieved by means of thyroid preparations. ERNOULD[146] saw temporary improvement, but no lasting result, from oral administration of thyroid preparations combined with X-ray treatment of the pituitary gland

ULLRICH and WIEDEMANN[216] propose that investigations should be made concerning the influence of injections with hyaluronidase on Reilly's granules and on the histological changes in liver and spleen.

hydrocephalus to obstructions resulting from bony changes of the base of the skull. According to PRICK * hydrocephalus has also been described as the result of aqueduct stenosis.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Diagnosis is stated to be difficult only in abortive forms or in the initial stage of the disease. As a differential diagnosis the following diseases are mentioned: rachitis, hypothyreosis[69, 165, 186, 236], and mongoloid idiocy, cleidocranial dysostosis, hyperplastic periostal dysostosis and Crouzon's hereditary craniofacial dysostosis[3]. Also pituitary dwarfism and chondrodystrophy, as well as arthrogryposis[274] are mentioned

KRESSLER and AEGERTER discuss some points of difference with the lipid and the glycogen storage diseases[29]. Whether Morquio's disease belongs to gargoylism, or should be differentiated as a separate syndrome distinct from the latter, is a question not yet answered unanimously. Both diseases are *characterised by an osteoligamentary syndrome. Morquio's disease is limited to this syndrome* The syndrome generally distinguishes itself in Morquio's disease, among others, by "hyperlaxite ligamentaire" of the joints of the *hands, more pronounced thoracic deformity, greater extension of the vertebral* anomalies and predominance of the skeletal changes in the lower extremities

Especially a more or less generalised platyspondylia (broad vertebrae) is seen, whereas in gargoylism the malformations remain limited to the thoracolumbar transition where microspondylia, spondylolysthesis and the absence of the anterior upper quadrant of the vertebral body ("fish-hook shape") are the most frequent findings These differences do not necessarily always occur. Platyspondylia occurs as an exception in gargoylism[30 72 190] and in Morquio's disease also the "fish hook shape" is occasionally seen

Although generally different, the skeletal changes, in so far as they can be seen by X-ray photos, may resemble each other so closely that most authors now assume that it is not possible to establish the differential diagnosis only by means of the X-ray picture[186 198]

Morquio's disease furthermore, distinguishes itself by the lack of accumulation symptoms. Neither is there a Hurler face In all publications on the differential diagnosis between gargoylism and Morquio's disease, it is mentioned that corneal cloudings are absent in the latter WIEDEMANN[249] doubts the correctness of this statement and quotes two Morquio cases *with* corneal cloudings, moreover the liver and spleen were found *to be enlarged* on palpation. He concludes from this that also in Morquio's disease deposits of pathological material may occur

Gargoylism and *Morquio's disease are sometimes considered as manifestations*

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* Oral information

are of opinion that neither Tay-Sachs' disease belongs to the lipidoses[283]. Personal opinion is that the conception, that gargoylism should belong to the lipidoses is only partially acceptable; it can only be maintained for the changes in the central nervous system

Furthermore, it should be remembered that the occurrence of these changes is not even imperative in gargoylism

Is Gargoylism an Endocrinopathy?

The general appearance of the sufferer of gargoylism in some respects resembles that of the patient with endocrine disorders. It must be attributed to this resemblance that investigators unfamiliar with the clinical picture sometimes wrongly diagnose it as infantile myxoedema or cretinism[89].

From the discussion following the demonstration by HUNTER[3] it appears that the possibility of an endocrine disturbance was considered Especially the premature plethoric appearance was thought to be remarkable in this respect HURLER thought a certain relationship with endocrine conditions to be present[3] NONNE[7] saw in his case a combination of "imperfekter Chondrodystrofie mit imperfekter Myxoedema infantile" (imperfect chondrodystrophy with imperfect infantile myxoedema)

SHELDON[19] described the picture as a "form of gigantism with splenomegaly" in a patient in whom too strong growth occurred instead of dwarfism REILLY[25] called the disease "an atypical familiar endocrinopathy with a syndrome of other defects".

ERNOULD[237] was struck by the discordance between the hypertrophy of certain organs on one hand, and developmental arrest or functional insufficiency of various organs on the other, and sees in this symptomatology the resultant of acromegaly and hypothyreodism, for which he considers a pituitary dysfunction responsible, or an altered sensitivity of the periferal tissues for hormones as the result of an enzymopathy

According to a statistical inquiry by A. GIAMPALMO and V GIAMPALMO [172], sella changes are observed in 50% of the cases, at post mortem an enlarged pituitary gland is seldom found. When the pituitary is large, the enlargement is generally adenohypophysial, and it is mainly the chromophobe cells that show gargoyle cell changes[39, 79, 81, 133, 154, 262, 263, 284].

Functional disturbances of the pancreas are not mentioned in the literature Sporadically sexual infantilism is described[7, 193].

The thymus gland is sometimes enlarged[25, 138, 281] DUHAMEL denies that in gargoylism glandular disturbances should play a part[107] Some regard the dwarfism and the skeletal changes as manifestations of an endocrine dysfunction Others appreciate the errors of growth as primary results of metabolic disturbances localised in the connective tissue itself[133, 209].

In cretinism radiological changes of the spinal column may occur showing a resemblance to those seen in gargoylism, which may make it difficult to

Chapter II

CRITICAL REMARKS WITH REFERENCE TO THE LITERATURE

Is Gargoylism a Lipidosis?

The discussion in the literature on the question whether or not gargoylism belongs to the lipidoses is extremely lively and, in fact, undecided.
In favour of the opinion that gargoylism belongs to the lipidoses is the fact that in this disease all typical ganglion cell changes are found, such as are described in certain forms of lipidosis (Niemann-Pick and Tay-Sachs) as well as the particular relationship in histochemical and biochemical respect, to the Tay-Sachs' disease. Indeed in both diseases there are indications for the supposition of ganglioside increase, on the ground of an excess of hexosamine and neuraminic acid in the brain tissue.
Also the conviction of some investigators that the accumulation in the viscera and the nervous system is attributable to a metabolic disorder of the glycolipids could be used as an argument in favour of this conception
A counter-argument is the opinion — strengthened by experiment — of some investigators that gargoylism is primarily a disorder of the metabolism of complex carbohydrates which co-incides with accumulation LINDSAY injected rabbits intravenously with macromolecular carbohydrate and then saw changes arising (in intestines and cornea) resembling those of gargoylism [112].
Similar experiments were also made by HUEPER and TOLENTINO in cooperation with TERRAGENA [285]. The latter two discovered that, if very young rabbits are subjected to these experiments, besides thesaurismotic change in the liver and cornea, also chondrodystrophic changes may appear [285]
The occurrence of hexosamin both in mucopolysaccharides and in gangliosides, according to some investigators, also pleads for a primary disturbance in the metabolism of the combined carbohydrates.
Moreover, as a further argument is the fact that in quantitative chemical examination some investigators have found no increase of the percentage of lipids in the viscera.
The reticuloendothelial system is regularly affected in a considerable measure according to HENDERSON et al [201]. Other investigators deny this and consequently reject gargoylism as a lipidosis For similar reasons they

are of opinion that neither Tay-Sachs' disease belongs to the lipidoses[281]. Personal opinion is that the conception, that gargoylism should belong to the lipidoses is only partially acceptable, it can only be maintained for the changes in the central nervous system.

Furthermore, it should be remembered that the occurrence of these changes is not even imperative in gargoylism

Is Gargoylism an Endocrinopathy?

The general appearance of the sufferer of gargoylism in some respects resembles that of the patient with endocrine disorders. It must be attributed to this resemblance that investigators unfamiliar with the clinical picture sometimes wrongly diagnose it as infantile myxoedema or cretinism[69].

From the discussion following the demonstration by HUNTER[3] it appears that the possibility of an endocrine disturbance was considered. Especially the premature plethoric appearance was thought to be remarkable in this respect HURLER thought a certain relationship with endocrine conditions to be present[5] NONNE[7] saw in his case a combination of "imperfekter Chondrodystrofie mit imperfekter Myxoedema infantile" (imperfect chondrodystrophy with imperfect infantile myxoedema).

SHELDON[19] described the picture as a "form of gigantism with splenomegaly" in a patient in whom too strong growth occurred instead of dwarfism. REILLY[25] called the disease "an atypical familiar endocrinopathy with a syndrome of other defects".

ERNOULD[117] was struck by the discordance between the hypertrophy of certain organs on one hand, and developmental arrest or functional insufficiency of various organs on the other, and sees in this symptomatology *the resultant* of acromegaly and hypothyreodism, for which he considers a pituitary dysfunction responsible, or an altered sensitivity of *the periferal tissues for* hormones as the result of an enzymopathy.

According to a statistical inquiry by A. GIAMPALMO and V. GIAMPALMO [172], sella changes are observed in 50% *of the cases*; at post mortem an enlarged pituitary gland is seldom found. When the pituitary is large, the enlargement is generally adenohypophysial, and it is mainly the chromophobe cells that show gargoyle cell changes[39, 79, 81, 133, 144, 262, 263, 284].

Functional disturbances of the pancreas are not mentioned in the literature. Sporadically *sexual infantilism is described*[7, 193].

The thymus gland is sometimes enlarged[25, 138, 258]. DUHAMEL denies that in gargoylism glandular disturb*ances should* play a part[107]. Some regard the dwarfism and the skeletal changes as manifestations of an endocrine dysfunction Others appreciate the errors of growth as primary results of metabolic disturbances localised in the connective tissue *itself*[133, 209].

In cretinism radiological changes of the spinal column may occur showing a resemblance to those seen in gargoylism, which may make it difficult to

establish the differential diagnosis of cretinism by means of the X-rays [69, 165, 186, 236].

In gargoylism the ossification of the metacarpal centres is sometimes delayed [2].

Several investigators consider that in gargoylism secondary endocrine disturbances are present, due to the affection of the endocrine apparatus by the same metabolic disturbances occurring in the other organs.
Hormone determination in the urine is hardly mentioned in the literature, so that it is not yet clear what value should be attached to the fact that pathological findings have been noted in this respect.

The corneal cloudings seen in respect to the differential diagnosis with Morquio's disease.

The presence or absence of corneal cloudings is considered an important differential diagnostic criterium between gargoylism and Morquio's disease.
According to the general opinion, the occurrence of corneal cloudings excludes the diagnosis of Morquio's disease.
Both conditions resemble each other in great similarity of the osteoligamentary syndrome.

The main point of difference is that gargoylism is coupled with storage manifestations and the disease of Morquio not. To the present day post mortems (3 in all) [115 133 186] of patients with Morquio's disease, have indeed not revealed any storage manifestations.

Hepatosplenomegaly owing to accumulation has not been found in Morquio's disease Apparent enlargement of liver and spleen, however, is described as the result of displacement by strong thorax deformity or through other causes [115 235]. There are cases of Morquio's disease on record in which corneal cloudings became visible only at an older age, and consequently (corneal cloudings being considered as storage manifestations) the diagnosis changed into gargoylism [9 22 41, 42 73 97 145 338]. *This form of gargoylism is known in the* literature as "Spat-Hurler" type of gargoylism
WIEDEMANN [219] counts these cases under Morquio's disease, as he is of opinion that Morquio's disease may also be coupled with symptoms of accumulation.

There are also investigators who see gargoylism, Morquio's disease and the so-called "Spat-Hurler" type as manifestations of one disease [132 157 167 262], these investigators maintain the difference between the Morquio type and gargoylism on the basis of the presence or absence of accumulation symptoms.
In support of this view they quote BÜCKER [77] who stated that in several families Morquio and Hurler cases were observed simultaneously Later on all of these proved to be "Spat-Hurler" cases, in which the members of the family who presented a Morquio-like osteoligamentary syndrome were looked upon as Morquio-cases and the others — presenting the same syn-

drome, but in whom afterwards corneal corneal cloudings were found, — as cases of gargoylism[9, 22, 41, 42, 73].
McKUSICK, as the result of personal experiences, doubts whether both af*flictions* have occurred in one family[274].
On histological examination of the bony and cartilageous tissue in gargoylism and in Morquio's disease the only point of difference, according to MAU, would appear to be, that in gargoylism "gargoyle cell" changes are *sometimes* observed in these tissues and *never* in Morquio's tissues. This does not, according to MAU, exclude uniformity in the cause of the changes in the bony and cartilageous tissue in both diseases[316].
Returning to the view that corneal cloudings are a manifestation of accumulation, brought about by foam-like cells in Bowman's *membrane*, it should be mentioned that there are reasons to surmise that in *gargoylism it cannot* be taken for granted that the corneal cloudings should be accumulation symptoms
KRESSLER and AEGERTER[29], in a case of gargoylism attended with corneal cloudings, did not find any histological changes on examining the eye.
NEWELL and KOISTINNEN[269] found the cloudings to be most pronounced in the central part of the cornea, whereas the foam cells were chiefly found near the corneoscleral limbus. They consider it unlikely that these cells have any relation to the corneal cloudings They are more inclined to suppose that structural changes of the corneal connective tissue are in causal relation to the cloudings. BISHTON et al.[284] found no histological changes in the cornea (post mortem at the age of 6 years), in a typical case where corneal cloudings had been diagnosed (at 2 years of age).

Personal opinion is that it is of importance for the differential diagnosis that the pathology of the corneal cloudings should be elucidated. If the latter prove to be due to structural changes, then the Spat-Hurler type of gargoylism ought indeed to be counted as belonging to Morquio's disease (as WIEDEMANN considers for different reasons). However, should it appear that the prevalent opinion about the cause of corneal cloudings, namely, that they are to be attributed to accumulation, is correct, then this symptom can be maintained as an important differential-diagnostic criterium between Morquio's disease and gargoylism

It is, however, also conceivable that both factors — accumulation and structural errors — occurring either separately or combined, might result in the phenomenon of corneal cloudings. In the former case, the phenomenon would be of little value for the differential diagnosis, in the latter, it would keep its value, otherwise agreeing with the opinion of most investigators that there are sufficient differences between gargoylism and Morquio's disease to justify maintaining the two as separate syndromes for the time being[168, 186].
Both syndromes can be traced back to a hereditary metabolic change. It is, however, *still* unknown to what extent the metabolic changes in these two syndromes are mutually related.

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1. Psychic deterioration is a conspicuous symptom (McGILLIVRAY[181], LIESSENS[115]. Ventricular dilation in combination with hydrocephalus is often seen
2. Generally the patients do not get older than 10-15 years
3. Corneal cloudings are often observed
4. Here, too, serious forms of deafness may be found.
5. Sella widening is commonly seen, as well as kyphosis dorsalis
6. Here too, considerable enlargement of the liver is often seen, a strong positive Best-stain however in the minority of cases only.

Comparison of the classical picture with typus E — with a view to obtain an insight into the question which functional disturbances or phenomena are purely the sequelae of the neurolipidosis — gives rise to the following remarks:

1. Based on the obvious differences between typus E and the classical syndrome (the resp absence or prominence of psychic deterioration) it is acceptable indeed that the presence or absence of neurolipidosis may be decisive for the occurrence or absence of psychic deterioration. Absence of psychic disturbances does not exclude neurolipidosis as appears from some of the case histories and post mortems published by STRAUSS et al[123]. The part played by the hydrocephalus and/or the cerebral vascular or perivascular manifestations is not taken into account here.
2. The absence of neurolipidosis may be of importance for the prognosis.
3. That in the cases of typus E mentioned above no corneal cloudings have been observed, should not be attributed to the abscence of neurolipidosis, but to the fact that the greater number, possibly all, belong to the sex-linked inherited form of gargoylism in which corneal clouding does not generally occur. It is not believed that typus E is limited to the X chromosomal pattern of inheritance.
   The autosomal pattern of inheritance in cases where the *clinical picture* gives rise to the presumption that neurolipidosis is not present (prolonged life span, absence of psychic deterioration and hydrocephalus) have been repeatedly described in the literature[7 38 45 106].
   In several of these cases corneal clouding does occur. However, no post mortem was made, so that there is no *certainty* with regard to the question whether neurolipidosis is present or not.
   Typus E seems to be represented exceptionally strongly in the sex-linked group. This question will be further gone into in the chapter on the anthropogenetic aspects
4. Seeing that both in typus E and in the classical form serious deafness may occur, it is obvious that the cause of this deafness should not, in the first place, be looked for in the neurolipidosis
   This does not, of course, exclude the neurolipidosis as primary or secondary

There is, however, an objection to the view that Morquio's disease should be a forme fruste of gargoylism, because the skeletal changes are more conspicuous in Morquio's disease than in gargoylism, which is hardly compatible with the view of it being a forme fruste.

TYPUS E - (GARGOYLISM WITHOUT NEUROLIPIDOSIS)

Owing to the accumulation of sphingolipids in the ganglion cells, KLENK, EDGAR and DIEZEL count gargoylism among the sphingolipidoses[29]. To the sphingolipids the following substances belong :– ganglioside, sphingomyelin and cerebroside.

According to these authors the following diseases belong to the sphingolipidoses.

I	Tay Sachs'	(accumulation of gangliosides)
II	Gaucher's	(„ „ cerebrosides)
III	Nieman-Pick's	(„ „ sphingomyelins)
IV	Gargoylism	(„ „ gangliosides)

For convenience sake the affection which is present in the nervous system in gargoylism will, in future, be called neurolipidosis. In gargoylism the neurolipidosis is not an obligatory affection, although mention should be made that it is not often absent. C de LANGE[104] was the first to observe that the neurolipidosis may be completely absent She made this discovery during the post mortem of a patient whose syndrome had shown some remarkable features (absence of the following signs. corneal cloudings, kyphosis and widening of the sella turcica), on which basis (in collaboration with WOLTRING) it was deemed advisable for the time being to set this syndrome apart from the classical form as Typus E.[34, 104].
Since then, similar observations have been made by WOLFF[83], SMITH et al[194], REILLY and LINDSAY[132] and BEEBE and FORMEL[218] in which also the absence of neurolipidosis was verified by post mortem.

A summary of the most important characteristics of these observations (i e of Typus E), follows.

1 Psychic deterioration and neurological changes were lacking.
2. The age reached (19-43 years) was considerably higher than the classical standard of gargoylism
3 Corneal cloudings were not observed.
4 Most patients showed a serious form of deafness
5. Sella widening was noted in this type, but in most cases it was absent The same is true of the kyphosis
6. In all cases the liver was greatly enlarged and in the majority of cases the Best-stain was strongly positive.

A comparison of these data with the classical syndrome of gargoylism (i e. coupled with neurolipidosis) now follows.

GARGOYLISM FROM THE ANTHROPOGENETIC POINT OF VIEW

From the outset gargoylism has been suspected to be a hereditary disease. Since the publications of HALPERIN and CURTIS[91], who showed it to be a recessive heredity determined by a single autosomal gene, this view has become an established fact

DE RUDDER[85 99] confirms that gargoylism is a recessive hereditary affection, but is of opinion that only the simultaneous presence of two genes (a "Morquio gene" and a "Phosphatid-diathesis-gene") produces this affection, while it is not yet clear whether both genes are situated in one chromosome

This conception is supported by BÜCKER[77], based on a probable occurrence of cases of Morquio's disease and of gargoylism in one family. ULLRICH[97] considers the disease a recessive hereditary affection based on a pleiotrophic gene. SCHINZ[93] sees in gargoylism and Morquio's disease a recessive hereditary affection determined by one gene with „polyphaner Manifestation und Subletalwirkung" (polyphany and sublethal action) WAARDENBURG[114] thinks it justified to class the disease among the recessively hereditary autosomal characteristics JERVIS[157], JANSSEUNE[212] and WIEDEMANN[240] are of the same opinion WOLFF[88] demonstrates the existence of a hereditary form of gargoylism linked to the male sex, while NJÅ[112] is the first to point out that in this type of gargoylism corneal cloudings are absent

On the strength of the data given in the literature, it may now be assumed that the following hereditary transmissions exist

A *Recessive Autosomal*

This form of hereditary transmission is characterised by the absence of symptoms in the parents of the patient, by its equal occurrence in female as in male members of the family and the high frequency of consanguinity, which increases the chance of concurrence of recessive genes.

pathogenetic factor in the classical form of gargoylism. C. de LANGE[104] found an atrophy of the organ of Corti, while WOLFF[88] gives the following description: "The organ of Corti preserved its normal contour, but no abnormal cells could be identified" (these two patients belong to typus E).

RICCI and ANCETTI[271] (in the classical form of gargoylism) found changes in the cochlear ganglion resembling neurolipidosis.

In any case, from this it is apparent that the conception of the deafness as a symptom of neurolipidosis[167] is not quite correct.

5. From the fact that the sella widening may occur in the Typus E as well, it appears that this symptom cannot, without any question, be considered as an exponent of the neurolipidosis.
6. The results of histo- and biochemical examination of the liver in the typus E and in the classical form merit comparison.

Sofar only observations of typus E confirmed by post mortem have been considered.

However, in the literature there undoubtedly figure more typus E cases in which the absence of neurolipidosis has not been verified by histological examination.

From the clinical picture alone it is not yet possible to conclude with *certainty* whether or not the disease is attended with neurolipidosis Some general rules, however, could be given.

A. The following symptoms are in *favour* of the presence of neurolipidosis.
   a Hydrocephalus,
   b Mental deterioration

   ad a: Although no observation is known in which hydrocephalus was found and neurolipidosis was not, yet the possibility ought to be taken into account that the two may occur separately

   ad. b: The possibility that mental deterioration in some cases where neurolipidosis is absent is brought about by vascular or perivascular processes in the brain, should be considered

B. The permanent absence of psychic deterioration does, it is true, justify the supposition that neurolipidosis is not present, but there is no guarantee to this.

Chapter III

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On the strength of the data given in the literature, *it may* now be assumed that the following hereditary transmissions exist:

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B. The permanent absence of psychic deterioration does, it is true, justify the supposition that neurolipidosis is not present, but there is no guarantee to this.

conditions are enumerated. vertebral changes and isolated occurring corneal cloudings[61], anomalies of the ribs[286], cranial hyperostosis and oligophrenia[305]. ULLRICH - WIEDEMANN[216] and BAMATTER - LAMY[305] looked in vain among the relatives of their respective recessive autosomal and X-chromosomal cases of gargoylism for such-like microsymptoms.

Returning to the statistical researches of HERNDON et al[254] they compile statistics on the frequency of certain clinical symptoms in a group of 96 cases of the autosomal type, and compare these with the frequency of the same clinical symptoms in a group of 21 cases of the X-chromosomal type and 129 cases of unknown genetic type (autosomal or X-chromosomal) with a view to tracing possible significant differences. For this statistical comparative investigation they select the following signs

corneal cloudings, dwarfism, deafness, limitation of movability of joints, gargoyle facial expression, cranial anomalies, hepatosplenomegaly, mental defect, changes in the vertebral column, herniae, short neck, otitis media occurring in the case history, hypertrichosis and an enlarged sella turcica.

As pointed out, in this manner significant differences are found with regard to corneal cloudings and deafness The X-chromosomal form, contrary to the autosomal type, is seen to be characterized by the absence of corneal cloudings and a significant increase of deafness LAMY et al arrives at these conclusions by means of a similar statistical comparative investigation[308]

With regard to the results of these investigations, the following remarks must be made

1 WIEDEMANN[145 249] has pointed out that corneal cloudings are only to be excluded with certainty by means of slit lamp examination. As this examination took place only in a small section of the number of cases from the limited X-chromosomal group, the possibility must be taken into account that in a number of these cases where this examination did not take place corneal cloudings have nevertheless been present.

The view that corneal cloudings would be absent in the X-chromosomal form can be considered as a rash and perhaps incorrect conclusion.

2 The predominance of deafness should be expected in the autosomal group if the already earlier quoted opinions of GUY, LERIQUE, TURPIN and LAFOURCADE[161 227] are correct.

Against the acceptance of a significant greater frequency of deafness in the X-chromosomal group the following objections are raised·

In the first place, in studying the small number of patients of the X-chromosomal type, it is noted that [illegible]

so many patients with a [illegible]

good mentality Deafness [illegible] that is quite simple to establish in patients with normal mentality. In many cases of gargoylism, however, owing to the mental deterioration, it is difficult or practically impossible to

B. Recessive X-Chromosomal

In this sex-linked form the morbific gene is transmitted by female members, whereas the symptoms are only observed in males (on account of absence of one X-chromosome in the male). The parents have no morbid symptoms.

It is important to point out here that the disposition to develop gargoylism is linked to the single pathogenic X-chromosomal gene or to the two pathogenic autosomal genes.

Having considered that only these two forms of hereditary transmissions occur, HERNDON et al and LAMY et al have calculated that in about two-thirds of the number of cases the transmission is determined to be recessive-autosomal and in one-third recessive X-chromosomal [254, 308]. GUY and LERIQUE [161] state that in cases with clear corneae, the individual clinical symptoms, as well as the radiological changes develop less strongly than in the cases with corneal cloudings.

TURPIN and LAFOURCADE explain this difference of intensity by concluding that the gene could exercise a quantitative effect: "le gargoylisme, maladie récessive autosomique, serait plus grave et sans doute plus précoce que la variété gonosomique, parce que toute maladie relevant d'un gène à l'état duplex, même récessif, apparait plus tôt et est plus expressive que la variété provoqués par un gène à l'état simplex. Cette opposition entre ces deux variétés de gargoylism serait un exemple de plus d'un fait déja note en pathologie héréditaire" [227].

HERNDON et al and LAMY et al, by means of statistics try to find significant differences between the frequency of the various clinical signs in the two genetic forms of gargoylism and arrive at the conclusion that the sex-linked form, not only distinguishes itself by the absence of corneal cloudings, but also by the considerably greater frequency of deafness (42.9% as against 5.2% in the autosomal form [254, 308]) In the recessive autosomal form *the occurrence of corneal cloudings is calculated to be 81.3%* [254], *in other words, one-fifth of the number of cases with recessive autosomal trans*mission also have clear corneae.

KLEIN *et al* [261] *think it noteworthy that* in some cases of the X-chromosomal type, skin changes were found with the same topographic distribution [195, 204, 305, 343] They wonder whether this is perhaps a phenotypical equivalent of the missing corneal affection.

Gargoylism is a disease with a deadly course The sufferer only occasionally reaches the marriageable age. It is, therefore, generally excluded that the patient transmits the pathogenic gene to posterity. Therefore, as there are no indications that the frequency is decreasing, it is *likely that gene mutation* plays a part in sustaining gargoylism as a syndrome. Relatives of sufferers from gargoylism have been examined for the presence of microsymptoms of the disease which might be interpreted as manifestations of the pathogenic gene being present in a heterozygotic condition. In the literature the following

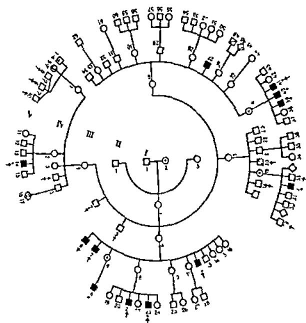


Figure 1 Ancestry of male sex-linked gargoylism

- □ Male sex
- ○ Female sex
- ○ Transmits the disease
- ■ Patient with gargoylism
- ⊠ Patient with probable gargoylism
- ◈ 4 Children of unknown sex
- Twins of uncertain identity
- ◇ Abortion
- + Dead under the age of 10
- . Examined personally
- . Examined by another investigator

males that died at an early age were not sufficient to diagnose gargoylism In V-14 the diagnosis was made on the ground of an extensive clinical examination undertaken elsewhere

V 18, 23, 32, 39, 40 and 41 were examined personally. In IV 6, 7, 12, 20, 27 and V 21 the description given by lay people suggested the diagnosis Of

establish exactly auditory disturbances. Therefore, it could be said that in the X-chromosomal group a greater number of cases occur in which, owing to the relatively favourable mental aspect and the more advanced age, it is possible to diagnose deafness

Moreover, it is important to consider the fact that both in the X-chromosomal and the autosomal group, - as was stated in the previous chapter - at least two different types of gargoylism occur: the classical form (coupled with neurolipidosis) and the typus E (characterised by the absence of neurolipidosis). It is conceivable that deafness is more frequent in the one type than in the other. Further it should be mentioned that up till now the typus E dominates in the X-chromosomal group.

If one really wants to establish whether the difference of heredity has any influence on the occurrence of deafness in gargoylism, then only the typus E cases from the X-chromosomal and autosomal groups have to be compared apart from the classical cases occurring in both groups

As this has not been done, it is doubtful whether the view, that deafness in the chromosomal group obviously occurs more than in the autosomal and that this symptom should be inherent to the way of transmission, is correct

Publications on families in which gargoylism is presumably inherited as a recessive X-chromosomal disease are now surveyed Such families have been described by WOLFF[88] NJÅ[112], LUNDSTRÖM[121], McGILLIVRAY[153], MILLMAN and WHITTICK[184], HOOPER[192], COLE et al[195], BEEBE and FORMEL[238], CUNNINGHAM[246], McKUSICK[274] and BAMATTER and LAMY[305]

In two cases the cerebrum was examined histologically without any changes being found. These cases concerned patients with normal intellectual faculties and a relatively advanced age (resp. 28 and 43 years).

Also the patients described by HOOPER[192] and McKUSICK[274] were intellectually normal. Those described by NJÅ, McGILLIVRAY and LAMY and BAMATTER, on the other hand, are characterised by serious and progressive dementia and the age reached, as in most cases of gargoylism, is not high

A relatively high age was reached by the patients described by WOLFF, HOOPER, COLE et al, BEEBE and FORMEL and McKUSICK

PERSONAL OBSERVATIONS

An opportunity occurred to examine some patients with gargoylism from a family in which the classical form of this disease occurs as a recessive X-chromosomal hereditary affection

In fourteen male relatives the diagnosis of gargoylism was established of which twelve certain and two probable It is possible that the actual number of cases in this family is still larger, because the available data concerning ten

1 Wolff[88]	4	III	28 yrs †	Normal	—	+	Typus E	Cerebrum, no changes
2 Njå[111]	8	II a	4 yrs	a Far below normal	—	+	Classic	
		b	11 yrs †	b Psychic deterioration	—			
		c		c Is able to walk, cannot walk	—			
3 Lundstrom[121]	1	IV	7 yrs 8 mths	Imbecility	—*		Classic	
4 McGillivray[183]	6	III	9 yrs	Psychic deterioration (I Q lower than 30)			Classic?	
5 Millman and Whittick[154]	6	III a	13 yrs 6 mths †	a Imbecility			Classic	Dilated ventricles
		b	16 yrs †	b Analphabetism				
		c.	21 yrs †	c Less strongly disturbed than a				
		d	25 yrs †	d Backward				
6 Hooper[192]			37 yrs	Normal	—	+	Typus E.?	
7 Cole et al[195]	1	II a	6 yrs		—	+	Typus E.?	
		b	23 yrs †		—		Typus E.	Cerebrum, no changes
8 Beebe and Formel[218]	9	IV	13 yrs †	Normal or moderately impaired			Classic?	
9 Cunningham[246]	12	III a	9 yrs 6 mths	Mental defect	—		Classic?	
		b.	8 yrs 3 mths	Mental defect	—		Typus E.?	
10 McKusick[274]	1	III	22 yrs	Normal.	—		Classic?	
11 Bamatter and Lamy[105]	6	III	7 yrs	Very pronounced retardedness	—		Classic	
12 the author	11	II a	6 yrs 10 mths	Psychic deterioration.	+		Classic	
		b	3 yrs 3 mths	Psychic retardedness.	—		Classic	
		c.	5 yrs 6 mths	Psychic deterioration	—*		Classic	
		d	8 yrs 2 mths	Psychic deterioration.	—*		Classic	Dilated ventricles.
		e.	5 yrs 6 mths	Psychic deterioration	—*		Classic	Dilated ventricles.
		f	1 yr	Psychic retardedness	—*			Typical cerebral changes, but no dilated ventricles, were found on post mortem …

* Verified by slit lamp examination

IV 27 and V 49 there was, moreover, a photograph available, which simplified establishing the diagnosis A detailed description of the alterations found in six of these patients, is given elsewhere in this publication (See Chapter IV, case I up to VI).

Of fourteen patients five are still alive:

V 18 — 6 months	V 40 — 9 years
V 32 — 8 years 3 months	V 49 — 1 year
V 39 — 11 years	

and nine dead:

IV 6 — 4 years	V 14 — 3 years 6 months
IV 7 — 9 years	V 21 — 3 years 9 months
IV 12 — 1 year	V 23 — 6 years 11 months
IV 20 — 13 months	V 41 — 2 years 9 months
IV 27 — 5 years 6 months	

The main data concerning these patients may be summed up as follows:

1. *Gargoyle facial expression.*
2. Large skull circumference.
3. Oligophrenia, at a later age together with progressive dementia and neurological signs.
4. *Hepato-splenomegaly.*
5. Typical skeletal changes and ligamentary contractures
6. Once (V 14) a slight corneal clouding was diagnosed In several cases corneal cloudings could be excluded by slit lamp examination
7. On caloric stimulation of the labyrinths no vestibular reaction was seen Disturbances in auditory functions could not be exactly determined on *account of psychic disorders*
8. Reilly's anomaly could not be shown.
9. The skin anomalies described by COLE et al, ANDERSSON - TANDBERG and LAMY - BAMATTER were not found in these cases

In the cases examined the symptoms manifested themselves early (before the third year of life) so that here an "early" form of gargoylism can be assumed Some relatives not suffering from gargoylism were examined for the presence of microsymptoms of the disease (IV 24, V 38, 42) The result of this examination was negative.

For the sake of completeness let it be noted here that in V 42 a slight choreiform restlessness and genua recurvata were observed.

A list of data from the literature and patients personally examined with male sex-linked gargoylism:

Chapter IV

CLINICAL CASE REPORTS

CASE I

BOY A Ancestry, Fig 1, V 23, Picture Fig 2 and 3

EXAMINATION (Age 6 years 10 months)

Data about the past history are lacking
The child, recently admitted to a home for mentally deficient children, shows on inspection the following features
A for gargoylism typical facial expression, an enlarged head and ears, marked hypertelorism, a broad and sunken nose root, a large protruding tongue, red cheeks, a broad and short neck, a broad thorax with sunken sternum, a protruding abdomen with an umbilical hernia, a considerable kyphosis present at the thoracic lumbar junction,



Fig 2
Case I, boy A, age 6 yrs 10 mths

Comparison of the literature data with personal observations leads to the following conclusions:

1. Contrary to the literature it is thought that in sex-linked gargoylism corneal cloudings may occur, although less frequently and in a mitigated form.
2. Up till now the X-chromosomal group comprises a relatively large number of patients of whom it may be supposed - taking into account the absence of mental disturbances and neurological signs - that there is no cerebral localisation of the disease (Typus E).
3. It is not considered proven that in the X-chromosomal group deafness occurs more than in the autosomal group.

Finally it should be remarked that the findings of FALCHI and MIDULLA [324] viz. that the average span of life is 11 yrs for males and 8 yrs for females, may possibly point to a more favourable course of the homozygous condition, as this condition is supposed to be present in half of the males [254, 305].

Chapter IV

CLINICAL CASE REPORTS

CASE I

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A for gargoylism typical facial expression, an enlarged head and ears, marked hypertelorism, a broad and sunken nose root, a large protruding tongue, red cheeks, a broad and short neck, a broad thorax with sunken sternum, a protruding abdomen with an umbilical hernia, a considerable kyphosis present at the thoracic lumbar junction,



Fig 2
Case I, boy A, age 6 yrs 10 mths



Fig. 3. Case I, boy A, age 6 yrs 10 mths

short and broad hands and fingers, flexion contractures of arms and legs — the fingers are crooked and the feet held in a pointed position —, increased hairgrowth at the back and the extensor sides of the extremities and acrocyanosis. The corneae are clear Further examination reveals a greatly enlarged liver and a less pronounced enlargement of the spleen No cardiovascular abnormalities The mouth contains, due to difficulties in swallowing, much saliva The pharynx reflex is low
There are signs of a spastic diplegia, predominating in the lower extremities
On both sides Babinski's sign is present
There is a mental deficiency comparable to the severest form of imbecility



Fig 4
Angular kyphosis Spondylolysthesis
Fishhook-shape of L 1 and 2

X Ray findings:

Skull The skull is too high and broad The roof is thickened A bulgy frontal bone The sutures are closed No strenghtening of the impressiones digitatae. The sella is not enlarged The mastoids contain little air

Thorax The clavicles are hefty (especially on the sternal end) showing a definite S-shaped curve Broad and horizontally running ribs The ends of the lower ribs are narrowed The thorax is barrel-shaped.

Vertebral column (Fig 4) Angular kyphosis at the junction of the 12th thoracic and first lumbar vertebra There is a clear lysthesis to the front of Th 12 in relation to L 1 Concave front of Th 11 and 12 Fishhook shape of L 1 and 2

Hand The first and second phalanges are cone-shaped Pseudoepiphysis at metacarpal I Broad and heavy metacarpals There are four ossified metacarpal centres visible

Biometrical data *

Laboratory findings: **

Before a more detailed examination had been carried out, the child died as the result of pneumonia at the age of 6 years 11 months

CASE II

BOY B Ancestry, Fig 1, V 14***

PAST HISTORY:

No details are known about his birth Normal dentition Started walking when he was 17 months old

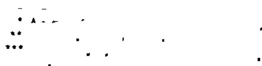
EXAMINATION. (Age 3 years 3 months).

The facial expression is typical of gargoylism The head is large and the root of the nose sunken The conchae of the ears are coarse The tongue hangs out of his mouth The tonsils are enlarged There is a *slight clouding* of the cornea on both sides There are no opacities of the lens The intra-ocular tension is normal Slit-lamp examination is not possible as the result of the poor co-operation of the child Heart and lungs are found to be normal The liver is enlarged The spleen is just palpable There is a large umbilical hernia Genitals no special features The hands are short and broad, the nails short and curved *in two directions* The back shows an extensive diffuse hair-growth

The child makes a *friendly* but stupid impression He is cheerful, laughs a great deal, plays continually and tries to seek contact It is not clear whether he can hear normally He does not talk yet and cannot understand the spoken instruction. On the whole he gives an impression to have a mental age of about two years

X Ray findings

Skull The skull-wall is fairly thick The frontal bone is prominent The distance of the ala magna to the base of the nose is too small The sella is not enlarged The mastoids contain little air



W K



Fig 3 Case I, boy A, age 6 yrs 10 mths

short and broad hands and fingers, flexion contractures of arms and legs — the fingers are crooked and the feet held in a pointed position —, increased hairgrowth at the back and the extensor sides of the extremities and acrocyanosis The corneae are clear. Further examination reveals a greatly enlarged liver and a less pronounced enlargement of the spleen No cardiovascular abnormalities The mouth contains, due to difficulties in swallowing, much saliva The pharynx reflex is low
There are signs of a spastic diplegia, predominating in the lower extremities
On both sides Babinski's sign is present.
There is a mental deficiency comparable to the severest form of imbecility.



Fig. 4
Angular kyphosis Spondylolysthesis
Fishhook-shape of L 1 and 2

The neck is short and broad
Heart and lungs are normal Normal E.C.G Blood-pressure 125/80. There is a small umbilical rupture The liver is enlarged The spleen is not palpable



Fig 6 Case III, boy C, age 8 yrs 3 mths

The hands are short and broad The end phalanges of the fingers are kept in a curved position The little finger is curved in a radial direction The nails are normally shaped There are no anomalies of the hair growth, neither is there acrocyanosis

Neuro psychiatric Examination (Age 5 years 5 months)

The motor functions of the cranial nerves are intact Speech is impaired and restricted to some hardly audible words
The musculature is normally developed. The power of the muscles does not show anything abnormal No fascicular contractions are observed The patient shows stereotype movements of which the following are the most important rhythmic swing movements of the trunk, continuous walking to and fro with the arms on his back and running with the arms extended in front of his body While running he makes screaming noises The movements are characterised by a lack of grace and suppleness Apart from this, there is apraxia, which is obvious from the continual trying of certain actions which, a few months ago, he could still perform
The sensibility cannot be judged exactly There is no ataxy when walking or standing. The gripmovements are well co-ordinated There are no tremors Spontaneous nystagmus is not present while the optokinetic nystagmus can be activated in both directions The pupils are of a middlewidth, equal in size and react well to light and convergence The oculopalpebral reflex is clearly strengthened and the reflexogenous zone is extended to the back of the head
The corneal - masseter and [illegible]
and cre [illegible]
The Tr [illegible]
The tone of the musculature is normal The cog-wheel phenomenon is absent When anxious sometimes an affective loss of tone occurs Eyesight and hearing cannot

Hand· The first and second phalanges are cone-shaped There are two hand-root nuclei visible

The child died some months later from complications arising from an operation for umbilical rupture

CASE III

BOY C· Ancestry, Fig. 1, V 32, Picture Fig 5, 6 and 7

CASE HISTORY:

Delivery was slow. At birth it was observed that the head was large and the forehead prominent

The hair on the head, which was originally shiny and curly, became bristly The closing of the fontanelles was delayed.

The development of the earliest childhood expresses itself in the following data sitting 5/12, first teeth 12/12, walking 13/12 When 18 months old, he could speak some words, but since then there was no further progress

He often had colds and bronchitis

Due to his aggressiveness he was admitted to an institution for mentally deficient children

FIRST EXAMINATION. (Age 5 years 5 months)

His head is relatively too long The forehead is prominent A cracked pot sound is present The facial expression is typical for gargoylism

The eyebrows are grown together, above a sunken nasal root The conchae of the ear are large There is a macroglossia The teeth are small and far apart The voice is high-pitched

The colour of the cheeks is of a bright red as the result of great dilatation of the skin capillaries

On both sides the corneal diameter of the eyes is normal All layers of the cornea are of normal clearness (slit-lamp examination) The fundi oculi are sound



Fig 5
Case III, boy C, age 8 yrs 3 mths

The neck is short and broad. Heart and lungs are normal Normal E.C.G Blood-pressure 125/80 There is a small umbilical rupture The liver is enlarged The spleen is not palpable.



Fig 6. Case III, boy C, age 8 yrs 3 mths

The hands are short and broad The end phalanges of the fingers are kept in a curved position. The little finger is curved in a radial direction The nails are normally shaped There are no anomalies of the hair growth, neither is there acrocyanosis

Neuro psychiatric Examination (Age 5 years 5 months)

The motor functions of the cranial nerves are intact Speech is impaired and restricted to some hardly audible words
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The corneal - masseter and pharynx reflexes can be normally activated The abdominal and cremasteric reflexes are lively as well as the periosteal reflexes of the extremities The Trommer reflex is absent Cloni cannot be evoked Normal footsole reflexes The tone of the musculature is normal The cog-wheel phenomenon is absent When anxious sometimes an affective loss of tone occurs Eyesight and hearing cannot

exactly be determined. On caloric vestibular stimulation not a single reaction is observed.

The development of the intellectual functions is retarded The level obtained is comparable with severe imbecility Memory and imprint are insufficiently developed and even *have deteriorated Speech - until recently the patient spoke a few words -* shows a recession Until recently the game still contained constructive elements, but now the patient shows no real interest in his toys. He only picks them up to throw away. His attention can only be drawn for a short time by a moving object

The recognition of persons is limited to those who look after him daily. The affectivity *is greatly influenced by factors in his surroundings. He is excitcable He seeks* contact with adults and laughs as soon as they look at him He has no interest in children



Fig 7
Case III, boy C, age 8 yrs 3 mths

There is little variation in his feelings and also little depth The instinctive behaviour can be classified as amorphous The spatial orientation is limited to the nearest surroundings He is still not clean

He likes to suck his fingers His sexuality is not present in a more differentiated form Hunger, thirst and sleep are normal His temperament is lively He has a great deal of energy and does not sit still for a moment. He particularly lives in a visual sphere There are no signs of manifest aggression towards his surroundings He gets soon frightened and is extremely dependant on those who take care of him He never looses sight of them His psychomotorism is poorly developed

Patient makes a clumsy impression which should be partly attributed to apraxia His *laugh is stereotype His crying makes a rudimentary impression and remains* limited to moaning The facial expression sometimes has a clown-like character

On examination he is not co-operative and automatically repulses forcefully everything that touches him He keeps on laughing at the physician who examines, but makes repulsive movements at the same time It is noticeable that he continues to laugh in a friendly way at the examiner to whom he objects This proves the inadequacy of his emotional expression

Electro-encephalographic examination

When the eyes were open only occasionally some parieto-occipital activity of 8/sec. was registered with moderate amplitudes A fairly strong beta activity was noticed, also in the posterior regions The sleep record was irregular, without asymmetry, sleep-spindles on both sides of 12/sec

On arousal a bilateral symmetric irregular activity of theta and delta frequencies was observed with a relatively high amplitude. Photic-stimulation was followed by a pronounced occipital driving response in the frequency range of the alpha and beta rhythm The E.E.G was judged to be diffusely disturbed to a slight degree.

Joints

Shoulders· The abduction, elevation and endorotation are limited The exorotation is normal

Elbows Flexion, extension, pronation and supination are limited

Wrists The movements in all directions are limited

Fingers The extension is limited.

Hips The flexion and adduction are good The following movements are limited. extension, endorotation and exorotation The abduction is slightly restricted

Knees Flexion and extension are limited

Ankles The ankle movements are normal

Toes Extension-restriction is similar to that of the fingers

X Ray findings

Skull Dolichocephalic form of skull Normal thickness of the skull wall The frontal bone is prominent The sutures are closed The sella is shoe-shaped and slightly enlarged The mastoid contains little air

Thorax The clavicles are strong The ribs are broad and have a horizontal course The extremities of the lowest ribs show a narrowing Barrel-shaped thorax

Vertebral column The lowest vertebrae are broad and flat. Intervertrebral discs are narrow, specially between L 1 2 Slight kyphosis at the level L 1 2 Anteriorly Th 11 and 12, L 3, 4 and 5 are concave

Pelvis The alae are too flat

Femur Coxae valgae The head of the femur is medially flattened

Hand The first and second phalanges are cone-shaped Pseudoepiphysis at metacarpal I Broad and plump metacarpals There are four ossified carpal centres visible

SECOND EXAMINATION, (Age 8 years 3 months)

The face has become thicker and has a more round aspect The corneae are still clear A reaction is noted only to loud sounds Speech has become worse The masseterreflex is lively The pharynx reflex is low There is now a slight spastic tetraparesis accompanied by hyperreflexia.

On both sides an ankle clonus can be elicited. The Babinski reflex is present The reflex of Trömmer is bilaterally slight positive Patient walks with his feet pointed The to and fro movements are not abolished No cog-wheel phenomenon is present During walking no ataxia is observed.

The behaviour of the patient is still hyperkinetic

In comparison with the previous examination it is, however, noticed that the patient does not like walking any longer He gives the impression that he gets tired very quickly He still seeks contact with adults but does not recognize them Toys do not interest him, not even to throw them away When eating he does not even try to hold his spoon The child continually sucks his fingers, while he is orally aggressive towards his clothes and chews them.

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The recognition of persons is limited to those who look after him daily. The affectivity is greatly influenced by factors in his surroundings He is excitable He seeks contact with adults and laughs as soon as they look at him. He has no interest in children



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On arousal a bilateral symmetric irregular activity of theta and delta frequencies was observed with a relatively high amplitude. Photic-stimulation was followed by a pronounced occipital driving response in the frequency range of the alpha and beta rhythm. The E.E.G. was judged to be diffusely disturbed to a slight degree.

Joints

Shoulders. The abduction, elevation and endorotation are limited. The exorotation is normal.

Elbows. Flexion, extension, pronation and supination are limited.

Wrists. The movements in all directions are limited.

Fingers. The extension is limited.

Hips. The flexion and adduction are good. The following movements are limited: extension, endorotation and exorotation. The abduction is slightly restricted.

Knees. Flexion and extension are limited.

Ankles. The ankle movements are normal.

Toes. Extension-restriction is similar to that of the fingers.

X-Ray findings:

Skull. Dolichocephalic form of skull. Normal thickness of the skull wall. The frontal bone is prominent. The sutures are closed. The sella is shoe-shaped and slightly enlarged. The mastoid contains little air.

Thorax. The clavicles are strong. The ribs are broad and have a horizontal course. The extremities of the lowest ribs show a narrowing. Barrel-shaped thorax.

Vertebral column. The lowest vertebrae are broad and flat. Intervertrebral discs are narrow, specially between L. 1/2. Slight kyphosis at the level L. 1/2. Anteriorly Th. 11 and 12, L. 3, 4 and 5 are concave.

Pelvis. The alae are too flat.

Femur. Coxae valgae. The head of the femur is medially flattened.

Hand. The first and second phalanges are cone-shaped. Pseudoepiphysis at metacarpal 1. Broad and plump metacarpals. There are four ossified carpal centres visible.

SECOND EXAMINATION. (Age 8 years 3 months)

The face has become thicker and has a more round aspect. The corneae are still clear. A reaction is noted only to loud sounds. Speech has become worse. The masseterreflex is lively. The pharynx reflex is low. There is now a slight spastic tetraparesis accompanied by hyperreflexia.

On both sides an ankle clonus can be elicited. The Babinski reflex is present. The reflex of Trömmer is bilaterally slight positive. Patient walks with his feet pointed. The to and fro movements are not abolished. No cog-wheel phenomenon is present. During walking no ataxia is observed.

The behaviour of the patient is still hyperkinetic.

In comparison with the previous examination it is, however, noticed that the patient does not like walking any longer. He gives the impression that he gets tired very quickly. He still seeks contact with adults but does not recognize them. Toys do not interest him, not even to throw them away. When eating he does not even try to hold his spoon. The child continually sucks his fingers, while he is orally aggressive towards his clothes and chews them.

BOY D: Ancestry Fig. 1, V 39, Picture Fig 8 and 9

CASE HISTORY:

Normal birth on time.
Data from childhood. tonsillectomy, operation for umbilical hernia, recurrent colds, measles and bronchopneumonia.
Could sit at 18 months, walk at 2 years 3 months, could talk from his 3rd year
Patient has only learned to speak a few words From his third and a half years he has gained no fresh knowledge, and deteriorated gradually
He has never been clean Owing to his temper and attacks of fury, he was admitted to an institute for mentally deficient children. The last two years it was noticed that he became abnormally dull and thirsty Now, however, he hardly eats and drinks. A few months ago he broke his lower left leg, since then patient cannot walk without support although healing of the fracture was successful



Fig 8
Case IV, boy D, age 11 yrs

FIRST EXAMINATION: (Age 8 years 2 months)

The facial expression is typical for gargoylism The hair of the head is dry and bristly and the margin of the hair irregular The conchae of the ears are large The nasal root is sunken Hypertelorism is absent The skin of the face is dry and scaly and the cheeks are red There is macroglossia The teeth are small and far apart On both sides the corneal diameter is slightly increased The retina and chorioidea show no abnormalities nor the macula lutea The papillae of the optic nerve are normal. In the corneae no particular substances or deposits are noticed (slit lamp examination) The eyelids are thick and flabby, causing the eye-slits to be narrow The neck is short and broad The thorax is broad, and it is noticeable that the centre part of the sternum is prominent Heart examination shows no abnormality The E C G. is normal The bloodpressure is 110/80 Bronchitic sounds are heard The abdomen is hefty, and there is a distinct hepatosplenomegaly Specially the liver is greatly enlarged. The genitals are normal The skin of the scrotum is thick The arms and legs are thin in comparison to the fat trunk and large head The lower

. . . ...cked fingers

limbs give a hypoplastic impression
The little finger is curved radially . . . the
An intense hair-growth is noticed . . . side of the extremities
lower limbs The skin is tense and on the back and extensor side of the extremities
squamous lesions are noticed. The subcutaneous fat-layer is strongly developed



Fig 9
Case IV, boy D, age 11 yrs

Neuro psychiatric examination (Age 8 years 2 months)

The motor functions of the cranial nerves are intact. The speech is impaired The muscles of the head, neck and trunk are normally developed The musculature of the extremities is hypoplastic, specially with reference to the distal parts The muscle power appears to be normal. No fascicular contractions are observed The patient has choreiform movements, the head keeps on moving and the attitude of trunk and extremities is continually changing. Noticeable is the frequent blinking of the eyes The patient is able to stand alone and with help to walk some steps He walks with his legs apart and drags them

The accompanying movements of the arms are not suspended during walking The sensibility is - as far as can be gathered - intact. There is no ataxia in standing or walking. There are no tremors Nystagmus is absent. The optokinetic nystagmus is normal

The pupils are of medium-width, equal in size and react well to light. The oculo-palpebral reflex is strongly positive The reflexogenic zone thereof is extended to the back of the head The patient reacts to loud sounds with an increased eye-blink reflex, also to menacing movements The corneal-, masseter- and pharynx reflex can normally be elicited

Primitive sucking and biting reflexes are observed

The mouth contains too little saliva The patient continually smacks his lips When

one wipes around his mouth, a spastic grin appears, at the same time his mouth opens The arm reflexes are lively; the Trommer reflex is negative. The abdominal and cremaster reflexes are low. The periost reflexes of the legs are not increased No pathological foot-sole reflexes can be elicited.

The muscle-tonus appears to be increased Sometimes it is possible to elicit an ankle clonus. Hearing and sight cannot exactly be determined. On caloric vestibular examination not a single reaction is observed In the examination of the intellectual functions, it appears that the development is very backward; the level reached compares with the severest form of imbecility, there is also a deterioration in the sense of dementia Memory and imprint are greatly disturbed. He only knows those who regularly look after him He is not interested in toys, and it is impossible to attract his attention even for a short period

The patient often makes a sleepy impression. Now and then he looks up and blinks a great deal with his eye-lids It is not possible to obtain an affective contact with the patient. His mood is apathetic and filled with feelings of disdain He just looks for a moment at adults and does not interest himself at all in children On coming closer to the patient, the motoric restlessness increases.

He sometimes produces a groaning noise The patient is completely dirty The satisfying of his desires has a definite oral character. Patient eats and drinks abnormally little and sleeps too much His attention is limited to the visual sphere The psychomotorism is poorly developed He has a fixed grin on his face Apart from this the patient makes a helpless and unhappy impression

Spinal fluid·

The pressure and composition of the fluid are normal

The colloidal tests (mastix, gold and benzoic acid) show a normal curve

The pneumoencephalogram obtained by lumbar insufflation shows a definite widening of the third and side ventricles

Electro-encephalographic examination

When the eyes were open no obvious alpha rhythm was observed The E E G contained many theta components of moderate amplitudes, as well as a fairly strong beta activity, also in the posterior regions.

On photic-stimulation a pronounced occipital driving response was seen, especially in the frequency range of the alpha rhythm The E E G was classified as to be diffusely disturbed to a slight extent

Joints:

The possibility of movement is restricted in many joints The scapulae are high In the shoulder-blades the abduction and elevation are restricted

The rotations are greatly restricted In the elbow joints all movements are diminished, as well as in the pulse In the hip joint all the movements are diminished, specially the adduction and endorotation, which are practically nil The flexion and extension in the knee joints are clearly restricted The toes are crooked, just like the fingers

X-Ray findings

Skull Brachycephalic form of skull The top of the skull is somewhat thin Deepened vascular impressions The sutures are open The entrance of the sella is enlarged The mastoids contain little air

Thorax Very massive clavicles (especially sternal) Broad ribs The extremities of the lower ribs show a narrowing, like a paint-brush The outline of the heart is normal Barrel-shaped thorax

Vertebral column Angular, right convex kyphoscoliosis at the level of the thora-

columbar junction The lumbar vertebrae are broad and have a concave margin in front whereby the lowest epiphysial plate is prominent (specially L. 2)
The lowest thoracic vertebrae have a concave front
Pelvis The ischial and pubic bones stand up-right and the alae of the iliac bone lie flat. The pelvis-ring is somewhat narrow at the level of the acetabuli Flat acetabuli Coxae valgae The head of the femur is medially flattened and the epiphyses have an irregular limit

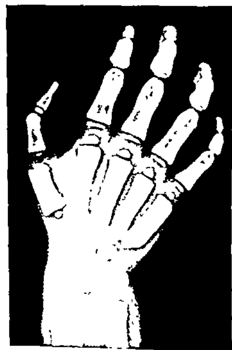


Fig 10
Cone-shaped phalanges
Broad metacarpals
Coarse trabeculation

Hand (Fig 10) Pseudoepiphysis at metacarpal I The phalanges are coneshaped There are four ossified carpal centres visible Broad and plump metacarpals
Foot (Fig 11) Coarse phalanges and metatarsals

SECOND EXAMINATION (Age 11 years)

Patient has now a distinct full-moon face
The corneae are still clear The hepatosplenomegaly has markedly increased There is still leukonychia. The masseterreflex is very lively [illegible]

[illegible] reaction is only on stimuli in the immediate neighbourhood, the patient reacts only to loud sounds
He now fails to recognize people



Fig 11.
Broad metatarsal I.

CASE V

BOY E. Ancestry, Fig 1, V 40, Picture Fig 12 and 13

CASE HISTORY.

Normal birth

The mental development was retarded Patient commenced to walk when he was 18 months old He has only learned to speak a few words Apart from recurrent colds and tonsillectomy, he has had no special illnesses or operations At the age of 4 years he was admitted to an institute for mentally deficient children

FIRST EXAMINATION (Age 5 years 6 months)

His facial expression is typically gargoyle The hair on the head is thick The eyebrows are grown together The ears are large The skin of the forehead and cheeks is red, dry and scaly Hypertelorism is absent The nasal root is sunken The teeth are small and far apart The tongue protrudes from the mouth There is no macroglossia Mucus comes from the pharynx and nose

The corneal diameter is normal The fundus is normal The lenses are clear As the child is frightened and restless the examination with the magnifying glass and slit-lamp is difficult No opalescence is found in the cornea, but it was not possible to exclude same with certainty

The neck is broad and short Heart and lungs are found to be normal The blood pressure is 125/80, and the E.C.G normal

The liver is greatly enlarged The spleen is only just palpable There is a thick

panniculus adiposis The abdomen is bulgy There is no umbilical hernia The penis and testicles are hefty
The skin of the back and extensor side of the arms is dry and scaly, and here the hair-growth is clearly intensified No acrocyanosis
The hands are short and broad, as well as the fingers which are crooked The little fingers are curved radially The nails are normal



Fig 12
Case V, boy E, age 5 yrs 6 mths



Fig 13.
Case V, boy E, age 9 yrs



Fig. 11.
Broad metatarsal I.

CASE V

BOY E: Ancestry, Fig. 1, V 40, Picture Fig. 12 and 13.

CASE HISTORY:

Normal birth.

The mental development was retarded. Patient commenced to walk when he was 18 months old. He has only learned to speak a few words. Apart from recurrent colds and tonsillectomy, he has had no special illnesses or operations. At the age of 4 years he was admitted to an institute for mentally deficient children.

FIRST EXAMINATION: (Age 5 years 6 months).

His facial expression is typically gargoyle. The hair on the head is thick. The eyebrows are grown together. The ears are large. The skin of the forehead and cheeks is red, dry and scaly. Hypertelorism is absent. The nasal root is sunken. The teeth are small and far apart. The tongue protrudes from the mouth. There is no macroglossia. Mucus comes from the pharynx and nose.

The corneal diameter is normal. The fundus is normal. The lenses are clear. As the child is frightened and restless the examination with the magnifying glass and slit-lamp is difficult. No opalescence is found in the cornea, but it was not possible to exclude same with certainty.

The neck is broad and short. Heart and lungs are found to be normal. The blood pressure is 125/80, and the E.C.G. normal.

The liver is greatly enlarged. The spleen is only just palpable. There is a thick

Elbows Flexion extension, pronation and supination are restricted The extension of the fingers is limited.
Wrists Movements are moderately limited in all directions
Back The back is flat There is no lumbar lordosis or scoliosis
Hips Flexion, extension, exorotation and endorotation is limited
Knees Extension and flexion are restricted
Ankles Movements are sub-normal

X Ray findings
Skull The skull wall is rather thin The sutures are open. Fairly prominent vascular impressions The distance of the ala magna to the base of the nose is too small The sella is shoe shaped and slightly enlarged.
Thorax The clavicles are hefty and the ribs broad The ends of the lowest ribs are narrowed (fig 14) The course is horizontal The sternum is prominent Barrel shaped thorax
Vertebral column There is a small bend at the level of L 1/2 The vertebrae are higher in front than at the back. In the thoracolumbar transition region the anterior side of the vertebral body is concave, while the distal epiphyseal plate is prominent
Pelvis (Fig 15) The alae are flat The acetabulum is flat and irregularly formed
Hip Coxae valgae
Knees Coarse epiphyses
Hands Coarse cone-shaped phalanges and metacarpals There are two ossified carpal centres visible Pseudoepiphysis at metacarpal I

SECOND EXAMINATION. (Age 8 years)

The motoric behaviour has deteriorated When he has to walk he sits down again immediately, he does sit up, however, when in bed There is motoric restlessness The upper part of his body moves rhythmically Patient still often whistles and also grinds his teeth
He is uncooperative during physical examination He keeps on laughing at the physician who examines him but in the meantime makes repulsive movements Eating on his own is no longer possible He does not show any interest even if the food is placed in front of him He grabs his spoon to throw it away. He has a great deal of interest in his nurse, laughs and tries to draw her attention He also shows an interest in his fellow patients. On neurological examination no changes are observed from the previous one

THIRD EXAMINATION: (Age 9 years)

The face is now emaciated The colour of the cheeks is now pale There is leuconychia of the finger- and toenails The motor functions have still further deteriorated. The patient can raise himself a little by leaning on the side of his elbow. He cannot walk or stand and only sits with aid His speech has entirely disappeared Swallowing is disturbed, he can only take fluids
The motoric restlessness has disappeared The pupils are narrow and only moderately dilate in the dark. The oculopalpebral reflex is too strongly positive The reflexogenic zone is extended to the back of the head
The pharynx-reflex is low The masseter-reflex is rather lively In eliciting same there also ensues a contraction of facial musculature Patient has stopped whistling nor does he grind his teeth. He yawns a lot There is a tetraparesis with moderate hypertonia and slight hyperreflexia. Babinski's reflexes are present on both sides It is possible to evoke a slight ankle clonus
The corneal and fundus examination shows no abnormalities On loud sounds the patient shows a slight reaction The intellectual functions have deteriorated Patient

Neuropsychiatric examination: (Age 5 years 6 months).

The motor functions of the cranial nerves are intact. Speech is limited to some word-sounds. The muscles of the head, neck, trunk and extremities are normally developed The muscle power is normal. No fascicular contractions are observed. There is a motoric restlessness, in the shape of rhythmic movements to and fro The movements lack suppleness. While walking simultaneous movements of the arms are observed The sensory functions seem not to be disturbed. There is no ataxia while walking or standing Tremors are not seen

Spontaneous nystagmus is absent. The optokinetic nystagmus can be elicited The pupils are of medium-width, equal in size and react well to light and convergence The oculopalpebral reflex is not increased The corneal-, masseter- and pharynx reflexes are normal Percussing the area round the mouth a tonic spasm arises in the facial musculature The arm, abdominal and cremaster reflexes do not show any abnormalities The periost reflexes of the legs are lively Cloni cannot be elicited The foot-sole reflexes are normal

The muscle tonus is good The cog-wheel phenomenon is absent The vision and hearing cannot be exactly determined. There is a reaction to loud sound stimuli On caloric vestibular examination no reaction is observed The intellectual functions show a retarded development From the past history it is also obvious that there is deterioration The level reached compares with the severest form of imbecility. In the past the patient was able to speak a few words Speech has now become inaudible and verbal contact is impossible. The memory and imprint function is insufficient The patient has an interest in toys The play-level is low He touches everything, opens what can be opened, and spreads the contents around him The duration of interest for each object is very short He also puts objects into his mouth Paper is eaten when he gets a chance Patient reacts when a hand is extended to him and then gives an impression of apraxia The emotional behaviour is unstable and in the highest degree dependant on factors in the vicinity His mood is excited and gay Noticeable is the stereotype whistling which increases when excited His laugh misses gradation and crying is limited to groaning He does not like being made a fuss of He knows how to orientate himself The state of cleanliness is not reached The urge to satisfy his hunger and thirst is small He has great passion for biting, licking or anything else of an oral character Patient grinds his teeth, yawns much and makes stereotype rhythmic movements

His sleep is not disturbed There is a certain interest in his fellow-patients He lives in a visual sphere There are no signs of manifest aggression He makes a clumsy impression which should be partly attributed to apraxia The psychomotorism is limited He has a fixed grin The facial expression is inadequate and often has a clown-like character On examination there is a lack of co-operation He defends himself automatically against any touch

Examination of the Spinal Fluid This does not show any abnormalities The colloidal curves (mastix, gold and benzoic-acid) show a normal pattern

The pneumoencephalogram obtained by lumbar insufflation shows a slight but clear symmetrical widening of the third and side ventricles

Electro-encephalographic examination

When the eyes were open no clear alpha rhythm was seen There was much diffuse activity of theta frequencies with moderate amplitudes

On photic-stimulation occipital driving was seen in the frequency range of the alpha rhythm The E.E.G was classified as to be without definite abnormalities

Joints

Shoulders *Abduction, elevation,* exorotation and endorotation are limited

no longer recognizes his nurse He has lost interest in his toys He makes a sad and helpless impression

During the day the patient sleeps a great deal but is often awake during the night His appetite has greatly diminished His personality has devitalized Patient still observes what happens in his immediate surroundings, but he sticks to details and does not recognise the people as such He grabs a hand in the same manner as he would grab an object He looks much older than his age

CASE VI

BOY T· Ancestry Fig 1, V 41.

PAST HISTORY:

Birth on time, delivery normal

Weight at birth 3000 gr

Apart from recurrent colds the patient has not been ill.

EXAMINATION. (Age 1 year) (Admission on account of acute otitis media)
The head is noticeably large The forehead is bulgy. The large fontanelle is still very open. The nose-root is sunken in The tongue is normal Two incisor teeth are visible The corneae are clear Heart and lungs are normal
The abdominal wall is flabby The liver enlarged The spleen is not felt The hands are short and broad and the fingers stubby The reflexes are normal

X Ray findings·

Thorax Hefty claviculae, specially at the sternal end
The ribs are strong and have a horizontal course The ends of the lowest ribs are narrowed The thorax is barrel-shaped
Vertebral column Arcuate kyphosis at the level of L 1/2
L 2 en 3 are fish-hook shaped
Pelvis Flat alae Flat acetabulum
Hips Coxae valgae and broadened neck of the femur.
Hands The first and second phalanges are cone-shaped Two hand roots are visible Broad and coarse metacarpals

Patient died as the result of broncho-pneumonia after measles, at the age of 2 years 9 months, in a home for mentally deficient children

CASE VII

BOY F

CASE HISTORY

Patient is the eldest of two children The brother also has gargoylism (see case VIII) Birth on time. Forceps delivery was performed after which a cyanosis of short duration ensued The weight at birth was 2500 *grams* There is no blood-relationship of parents The patient often had colds He was operated for an umbilical *hernia* A tonsilectomy was done

First teeth at 13 months, able *to sit at 18* months; walk at 2½ years, talk at 2½ years The patient had to be helped when eating His walking deteriorated gradually and now he can no longer walk without help.

EXAMINATION (Age 7 years 4 months).

The patient has a typical Hurler face The hair on the head is abundant and bristly The forehead is prominent There is hypertelorism The broadened nose has a sunken

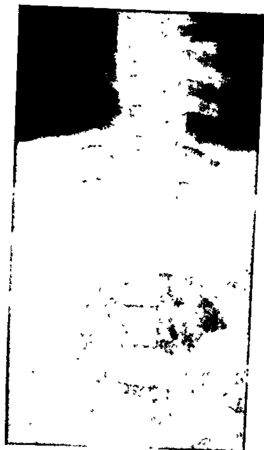


Fig. 14
Narrowed ends of the lower ribs.

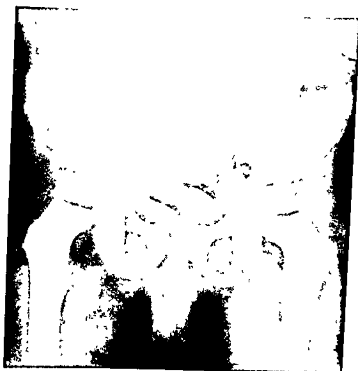


Fig. 15
Flat and irregular shaped acetabuli. Coxae valgae

...ands (Fig 16). Rough trabeculation of the phalanges and metacarpals. The phalanges are cone shaped Pseudoepiphyseal shaping at the distal end of the metacarpal I There are seven ossified carpal centres visible

Patient died, at the age of 7 years and 5 months, having been ill for a few days, of mucopurulent bronchitis



Fig 16
Cone shaped phalanges
Pseudoepiphysis at metacarpal I
Coarse trabeculation

CASE VIII

BOY H Picture Fig 17

CASE HISTORY

Patient is the youngest of two children The brother also suffers from gargoylism (Case VII)
Birth was on time by means of a Caesarean section
First teeth at 8 months, able to sit at 12 months, to stand at 13 months
At the age of one year the liver was enlarged

EXAMINATION (Age 1 year 5 months)

The facial expression is suspect for gargoylism The head is large The fontanel is wide open Light fair curly hair on his head. The black eyebrows are grown together above a broad and sunken-in nose-root The ears are large The cheeks are pale. The teeth are far apart. There is no macroglossia
No corneal cloudings (slit lamp examination) Normal fundi oculi Retarded pupil dilatation with homatropine
The neck is broad and short. Heart and lungs are normal.
The thorax is flat and broad The abdomen is fat and there is a small umbilical hernia

root The eyebrows are grown together. The ears are coarse. The colour of the cheeks is bright red. The widely-spaced teeth are small There is macroglossia and a noticeable hairgrowth on the upper lip
The corneae are clear (slit lamp examination). The corneal diameter is normal Normal fundi oculi.
The neck is short and broad. No cardiovascular abnormalities Lungs are normal The abdomen is balloon-shaped and there is an operation scar due to an umbilical hernia There is a diastasis of the rectus muscle of the abdomen The liver and spleen are greatly enlarged The femoral arteries pulsate well The testicles are small There is poor elasticity of the skin There is intensive hair growth on the shoulders and upper arms Acrocyanosis is noticed and leukonychia of the finger and toe nails

Neuropsychiatric examination: (Age 7 years 4 months)

In percussing the enlarged skull, a cracked pot sound is heard The motor functions of the cranial nerves are intact There is slight dysarthry The muscles show no abnormalities Patient can sit and stand, but can only walk with aid
The sensory functions cannot exactly be determined There is no ataxia Tremors are absent. Spontaneous nystagmus is absent The pupils react to light and are equal in size The corneal-, masseter- and pharynxreflexes are normal The periost reflexes of the arms and legs are lively Pathological pyramidal reflexes, as well as cloni are absent The abdominal and cremaster reflexes are weakly The cog-wheel phenomenon is absent. The visus and hearing cannot exactly be determined Patient reacts to strong sounds On caloric vestibular stimulation no reaction is observed
There is a retarded development of the intellectual ability The level can be compared with that of imbecility Patient produces repeatedly short senseless words The spoken word is not understood He shows no interest in what happens around him He is friendly and his behaviour apathetic He is not clean He continually smacks his lips Hunger, thirst and sleep are not disturbed The psychomotorism is poorly developed There is no gradation in his laughter, which makes the impression of a tense grin There is no co-operation on physical examination Touch is automatically resisted

Joints:

The distal phalanx of the fingers is in a flexed contraction The extension of the fingers is limited
In the elbows flexion and extension is limited The dorsal flexion of the pulse is diminished Limited abduction, elevation and endorotation in both shoulder joints Slight flexion contracture of the hips The abduction and exorotation are sufficient, but the endorotation is obviously diminished Genua valga Slight pes calcaneus The toes are in a varus position
Vertebral column slightly curved thoracolumbar kyphosis The whole vertebral column is stiff, including the cervical region

X-Ray findings:

Skull Large skull with prominent frontal bone The roof is thin and the sutures are open Fairly prominent vascular impressions The pneumatisation of the mastoids is defective The balloon-shaped sella is enlarged The occipital protuberance seems to be displaced downwards
Thorax Hefty clavicles The thorax is broad and the ribs are strong and follow a horizontal undulating course The ends of the third and fourth, as well as the eleventh and twelfth ribs are narrowed
Normal outline of the heart Barrel-shaped thorax
Vertebral column The lumbar lordosis is flat Slight curved kyphosis at the level of Th 12/L 1 The front of Th- 11, 12, L 1, 2 and 5 is dented in the middle

His temperament is slow. He is not tiresome He has a passive attitude He does not make any attempt to draw attention He can stand, but only tries it when stimulated to do so The child seems toe be capable of doing more than can be concluded from his spontaneous activities

The psychomotorism is poorly developed

The spinal fluid shows no deficiencies as far as pressure and composition is concerned The cell and protein content are normal. The flocculoreaction of proteins (gold, benzoic acid and mastixsol) shows a normal curve The pneumoencephalogram shows a symmetrical widening of the ventricular system

X Ray findings:

Skull. (Fig 18). The skull wall is thin. The large fontanel is open The frontal bone is prominent Rather prominent vascular impressions The sutures are open The shoe-shaped sella is enlarged The entrance of the sella is widened The mastoids contain very little air



Fig 18

Thin skull wall Large fontanel widely open Prominent vascular impressions Shoe-shaped enlarged sella, with widened entrance

Thorax Hefty clavicles The ribs are broad and run a horizontal course. The extremities of the lower ribs show a narrowing, like a paint brush Barrel-shaped thorax.

Vertebral column Slight kyphosis at the lever of Th 12/L 1 Fish-hook shape of Th. 12 and L. 1 The lumbar lordosis is flattened

Pelvis The pelvis is broad and flat The acetabula are normally shaped

Femur Coxae valgae The neck is broadened

Hands The first and second phalanges are cone-shaped Coarse trabeculation of the diaphyses There is an enlarged articular space between the metacarpals and phalanges Broad and plump metacarpals There are two hand-root nuclei

The liver is enlarged The spleen is not palpable The genitals are normal. The hands are short and broad, as well as the fingers There is a flexion contracture of the terminal phalanx of the little finger, which is radially curved. The nails are well shaped. There is no acrocyanosis The skin is somewhat pasty. The skin of the back is covered with black hairs The lumbar lordosis is flattened There are slight genua valga Slight flexion contracture in the hip joint

Neuro-psychiatric examination: (Age 1 year 5 months)

The motor functions of the cranial nerves are intact The speech is still undeveloped There are no abnormalities of the musculature There is no motoric restlessness Patient can stand and walk with aid As far as can be judged, the sensibility is intact There is no ataxia while walking or standing The grip-movements are also well co-ordinated There are no tremors Nystagmus is absent The optokinetic nystagmus is normal The pupils are of medium width, equal in size and react well to light The corneal-, masseter- and pharynx reflexes are normal The reflex examination of the extremities shows no special features The abdominal and cremaster reflexes are also normal Cloni cannot be elicited The muscle tone is unchanged The cog-wheel phenomenon is absent

The visus does not seem to be disturbed, neither the hearing



Fig 17
Boy H, age 1 yr 5 mths

The caloric vestibular stimulation produces a lengthened latency time, as well as a short nystagmus duration The intellectual level seems to be equal to that of a child of 11 or 12 months There are no signs pointing to deterioration The mood is friendly The instinctive behaviour is poorly developed The libido development in the psychoanalytic sense *is present in the oral phase Hunger, thirst* and sleep are definitely not disturbed

mental home for a lengthy period There is no blood relationship between the parents
The child had recurrent otitis media and nasal colds
Adenotomy was performed The stools were irregular (commencing with constipation, later the motions were thin) Twice she had (at the age of 10 months) an attack of screaming, accompanied by a tremor of the whole body
The birth was spontaneous and on time. The weight at birth was 2900 grams
Laughing 2/12, first teeth 7/12, sitting 8/12, standing 10/12.
From the tenth month onwards the development of the child was retarded

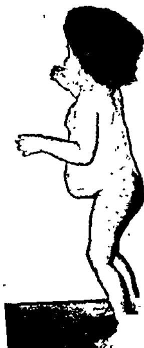


Fig 19
Case X, girl J, age 5 yrs 10 mths

FIRST EXAMINATION * (Observation from 2 years 3 months until 2 years 7 months)
The child has a very large skull and the forehead protrudes strongly, sunken-in nose root and hypertelorism The jaws strongly protrude forward. There is a cracked pot sound, the fontanel is not closed The hairs are thin and of varying colour The dentures consist of small, somewhat grey teeth which are far apart and stand in a broad proc alveolaris The palate is small and high The mouth is broad, the tongue is too large The pupils react to light The corneae are cloudy caused by a large number of dotshaped opacities These are spread through the whole of the parenchyma, from the membrane of Bowman to that of Descemet.

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* Prof Dr J P Slooff kindly gave us the case-history

GIRL I *

CASE HISTORY:

There is no blood relationship between the parents Patient is the eldest of 4 children The second one (a girl) has epilepsy and the youngest (a brother) probably suffers from gargoylism

The third child (a girl) died two days after birth with signs of cyanosis The mother had one miscarriage.

The patient was born by means of a forceps delivery At birth it was already noticed that the head was too large.

Patient suffered from parathyphoid and had often colds

She underwent adenoidectomy, tonsillectomy and was operated for umbilical hernia and for a polyp in the left nostril

She could walk and talk from about 18 months, from 3½ years onwards the psychic functions deteriorated It was also noticed that vision became worse From its 4th year the child was practically totally blind as the result of optic atrophy

EXAMINATION: (Age 5 years 9 months)

The head is very large and the forehead high and bulgy There is hypertelorism The back of the nose is broad and sunken The hair of the head is bristly and abundant. The lips are thick and the tongue too big The teeth are far apart The corneae are cloudy The pupil reactions appear to be normal

From the left nostril a small polyp protrudes

The right nostril also has polyps The nose septum is thin and possibly perforated The neck is short and broad The liver and spleen are obviously enlarged The upper arms and thighs as well as the shoulders are very hairy There is a lumbar scoliosis There are slight contractures of the arms and legs The foot-sole reflexes are indifferent

The tension on both arms is high, up to 200 140 The tension on the legs is much lower, about 60 mm systolic. The femoral arteries pulsate only slightly. Above the heart or the aorta no murmur is heard The E C G is normal.

X-Ray findings:

Skull The skull is noticeably large and elongated The wall is rather thick The sutures are wide open, excepting the lambda-suture which is invisible The mastoids contain very little air The sella is abnormally large, the anterior wall is missing

Thorax Coarse claviculae The ribs are broad and run a horizontal course The extremities of the lower ribs show a narrowing, like a paint-brush.

Vertebral column Slight kyphosis at the level of Th 12/L 1 Fish-hook shape of L 1, 3 and 4

Hands The first and second phalanges are cone-shaped Broad and plump metacarpals Seven ossified carpal centres are visible

CASE X

GIRL J: Fig 19

CASE HISTORY:

She is the second of four children The eldest was born prematurily and died at the age of 6 months MP had diabetes and on account of depression was nursed in a

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* Prof Dr J P Slooff kindly gave us the case-history

There is a reaction to sound stimuli Caloric vestibular examination was not carried out The psychiatric examination can be summed up as follows From the past history it is obvious that there is retardment in development, principally a lagging behind of the intellectual functions Later, on the basis hereof a dementia developed. Although



Fig.20
Enlarged, thin skull, with open sutures. Shoe-shaped, enlarged sella Distension of the occipital region



Fig 21
Fishbook shape of L 1 and 2
Kyphosis
Spondylolysthesis

the parents is not known A nephew (on father's side) died shortly after birth as the result of congenital brain anomaly

Patient was born by means of forceps (weight at birth 3160 gr.). At birth the skull appeared to be noticeably large. A variance of the back was also noticed (kyphosis) The tongue was large and furrowed The fontanel closure was normal

From the age of 16 months the girl could walk. Initially the mental development was fairly good, even though there was certainly a delay. The girl learned to speak but was never able to make sentences From her sixth year, speech gradually totally disappeared At the age of two the girl was clean at night, but later enuresis appeared She often had colds and pneumonia Tonsillectomy and adenotomy was performed At the age of 5½ years she was practically totally blind.

From the age of 6 she was completely bed-ridden From the age of 9 years, she regularly had epileptic fits

Patient has always been keen on music.

EXAMINATION: (Age 11 years 9 months)

The facial expression is typically gargoyle. Large, conspicuous long skull

The large auricles are implanted lowly There is hypertelorism The eyebrows are very developed, but are not grown together. The back of the nose is broad and sunken in The facial colour is bright red

There is macroglossia The corneae seem large and are cloudy. Consequently the pupil reactions cannot be determined.

The mouth contains a superfluous amount of saliva The pharynx reflex is nearly absent The teeth are carious Many parts are absent Those teeth which are left, are far apart The neck is short and broad

On physical examination of heart and lungs, bronchitic sounds are heard as well as a systolic murmer at the apex of the heart The abdominal wall is weak There is a diastasis of the rectus abdominal muscle There is an umbilical hernia The liver is greatly enlarged The spleen is not felt The vertebral column shows a kyphoscoliosis at the level of the thoracic lumbar conversion The skin of the back is very hairy The fingers are bent Apart from this the little fingers are radially curved The hands are short and broad The movements in the shoulder, elbow and hip joints are noticeably restricted There are genua valga

The nails are not malformed and are of a soft consistency

Neuro-psychiatric examination. (Age 11 years 9 months)

On percussion of the skull a cracked pot sound is heard Nystagmoid movements of the eye-balls are observed The muscles of the face are not paralysed

Patient cannot swallow normally and cannot talk The mouth contains a lot of saliva, probably as the result of disturbance in swallowing Repeatedly smacking movements are observed

The muscles of the neck and trunk appear to be normally developed The extremities, especially the distal parts, make an impression of hypotrophy, probably as the result of inactivity Fascicular contractions are not seen The power of the arms is clearly diminished The legs are paralysed

The sensory functions cannot exactly be judged Tremors are not noticed

As the result of corneal cloudiness the pupils cannot be examined The corneal reflex is normal The masseter reflex is very lively and the pharynx reflex is practically absent. The reflex examination of the arms does not show any abnormality The abdominal reflexes are low There is hyper reflexion of the legs On both sides foot sole reflexes of Babinski can be elicited *The feet are kept in a pointed position* The tone of the leg muscles is increased There is no cog-wheel phenomenon

The taste and smell function cannot be exactly determined Patient is totally blind

There is a reaction to sound stimuli. Caloric vestibular examination was not carried out The psychiatric examination can be summed up as follows: From the past history it is obvious that there is retardment in development, principally a lagging behind of the intellectual functions Later, on the basis hereof a dementia developed Although



Fig. 20
Enlarged, thin skull, with open sutures Shoe-shaped, enlarged sella Distension of the occipital region.



Fig 21
Fishbook shape of L 1 and 2
Kyphosis
Spondylolysthesis

it was not possible to examine the child anymore by means of psychological tests and to calculate and measure the intellect, it is definite that the child is gravely mentally disturbed This fact is obvious as no contact can possibly be obtained in the gnostic nor accoustic sphere

X-Ray findings:

Skull: (Fig 20) Large, especially long skull Thin skull wall The frontal bone is prominent The sutures are gaping The distance of the ala magna of the sphenoid to the base of the nose is small The shoe-shaped sella is enlarged.
Vertebral column. (Fig. 21) Fish-hook shape of L 1 and 2. Crack at the level of Th 12/L 1. Dislocation of L 1 in a dorsal direction
Thorax Broad clavicles and ribs. Ribs run horizontally The thorax is barrel-shaped
Humerus. The head of the humerus is flattened and irregular of shape The shaft of the humerus is very coarse
Hips Coxae valgae
Hands The first and second phalanges are cone-shaped Very broad hand Coarse trabeculation of the metacarpals There are 4 handroot nuclei visible

Patient died at the age of 12 *years as the result of starvation caused by not being* able to swallow.

CASE XII

*GIRL L **

CASE HISTORY:

She is an only child The birth was on time and was lengthy Patient often had a cold She was operated for an umbilical hernia She could sit at the age of 6 months Now, she can, with aid, make a few steps Two children of a sister of the mother (resp 15 and 16 years old), are supposed to have an affection of the thyroid gland

EXAMINATION (Age 14 months)

The facial expression is typically gargoyle The large fontanel is nearly closed
The auricles are large The eyebrows are grown together, above a sunken-in nose root The forehead is prominent
The eyelids are somewhat pasty The corneae are clear on both sides, also with slit-lamp examination The fundus is normal on both sides, also the papilli of the optic nerve and the macula region
The teeth and tongue show no abnormalities
Heart and lungs are found to be normal The neck is short and broad The abdomen protrudes and an operation scar is visible (umbilical hernia) The liver is just palpable, the spleen cannot be felt
There are small brown pigmentations to be seen at the level of the right shoulder and right inguinal region
The back is covered with black hair
The hands are short and broad The formation of the nails is not abnormal The little fingers are somewhat curved There is no acrocyanosis The lumbar lordosis has disappeared There is no restriction of joint movement Patient walks a few steps with aid, with legs far apart

Neuro-psychiatric examination (age 14 months)

No abnormalities are found There is, however, a weak reaction on caloric vestibular stimulation Patient shows a good reaction to sound stimuli

* Dr M L M Houben of Heerlen kindly gave us the opportunity to examine the patient

Electro-encephalographic examination

Only a sleep record could be obtained (seconal) No abnormalities were found.

X Ray findings

Skull Rather thin skull wall The frontal bone is prominent The sutures are open The large fontanel is not closed Increased impressiones digitatae The sella is slightly enlarged The entrance is slightly enlarged. The mastoids contain little air

Thorax Hefty clavicles (especially the sternal parts) Broad barrel-shaped thorax

Vertebral column Fishhook shape of L 1 and L 2

Pelvis Coxae valgae

Hands The first and second phalanges are cone-shaped Broad hands Broad and plump metacarpals There are four hand-root nuclei visible

CASE XIII

GIRL M Fig 22

CASE HISTORY

There is no blood-relationship in the family

The girl, which is an only child, was born normally and has had no special illnesses The sister of the mother suffers from a progressive affection of the nervous system, the nature of which is unknown



Fig 22 Case XIII, girl M, age 6 months

EXAMINATION (Observation age 5 to 7 months)

She has a typical Hurler-face

The large fontanel is still wide open The hair on the head is light blond and curly The auricles are large There is hypertelorism The colour of the face is pale The

corneae are cloudy in all layers on both sides. Basically this cloudiness is more pronounced The slit-lamp examination does not produce further details

The pupils dilate moderately with mydriatics. The fundus appears to be undamaged, but more delicate structural abnormalities could be camouflaged by corneal cloudiness The back of the nose is broad and sunken in The eyebrows are grown together. The shape of the tongue is normal The mouth is broad and the lips are thick Teeth are absent There are a few hairs on the upper lip

The liver is greatly enlarged. An umbilical hernia is absent The skin is sound. The trunk and extremities are hairy The lumbar lordosis is flattened and extension of the vertebral column is limited

Heart Examination.

The heart is enlarged 1 cm to the left. No praecordial bulging, no cyanosis and no thrill. When patient does not breathe a hard blowing systolic murmur is heard over the praecordium, with maximum intensity at the base of the heart. Low, along the left sternal edge hardly a murmur is heard The murmur is continued to the back, interscapularily. The second pulmonary sound is normal Many conducted sounds over the thorax The femoral artery pulsates far weaker than the brachial artery The tension of the left arm is systolically about 110, and that of the right leg about 70

Electro-cardiogram Normal axis Probably combined right and left hypertrophy.

Thorax Screening The heart is enlarged especially to the left The pulmonary arch is straight The filling of the lung is normal The progress of the aorta is to the left and the course of the oesophagus is normal

Neuro-psychiatric examination. (Age 6 months)

The motor functions of the cranial nerves are intact. The muscles are normally developed There is no motoric restlessness The sensory functions, as far as can be gathered, are intact Cerebellar function disturbances are not present The pupils are middle-wide and react well to light The oculopalpebral reflex is not increased Normal cornealmasseter and pharynx reflexes The reflex examination of the abdomen and extremities show no abnormalities

The muscle tone is normal There is a good reaction to light and sound stimuli The *caloric vestibular examination shows a long latency period as well as a short nystagmus* duration

The intellectual functions are certainly defective The motoric development is definitely retarded The head is not yet raised The actual graspmovement is not yet done by the patient, although some activity of the arm muscles is noticed The affectivity is not disturbed The appetite is small

The child has a friendly character The psychomotility is poorly developed

Electro-encephalographic examination.

There was no alpha-equivalent rhythm In its stead an irregular tracing was recorded consisting of varying theta-components whereon somewhat quicker activity was superimposed without constant asymmetry When crying, pronounced rhythmic activity of 3 per second ensued, above the posterior skull The E.E.G was very irregular without constant asymmetries It was classified as to be diffusely disturbed, to a slight degree

X-Ray findings:

Skull Thin skull wall The large fontanel is open The sutures are open The sella is not enlarged The mastoids contain little air

Thorax (Fig 23). The course of the ribs is horizontal Hefty clavicles (especially the sternal portion) The heart is enlarged to the left The thorax is barrel-shaped

Vertebral Column Kyphosis at the level of L 1/2 Fishhook shape of L 2 and L 3

Hands. Broad hand. The 1st and 2nd phalanges are cone-shaped Plump and broad metacarpals One ossified carpal centre is visible
Pelvis Subluxation of the head of the femur Coxae valgae.

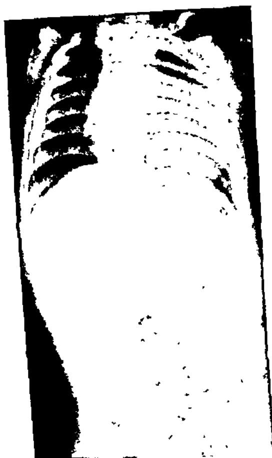


Fig 23
Hefty clavicles
Heart enlarged to the left
Hepatomegaly

CASE XIV

GIRL N Fig 24

CASE HISTORY

There is no blood relationship between the parents Patient is the fourth of five children, of which the eldest (boy) died at the age of 7 months as the result of an acute stomach and intestinal catarrh and the youngest (boy) died, eleven hours after a breach presentation, probably as the result of erythroblastosis foetalis The mother had three miscarriages (no rhesusantagonism)

The birth of the patient was normal She could walk at the age of 16 months, and was clean in time She underwent a tonsillectomy

EXAMINATION (Age 4 years 2 months)

The facial expression is gargoyle

The skull is too large The large fontanel is closed No bony ridges are felt on the

skull The forehead is prominent. The hair on the head is thick, stiff and shiny. There is hypertelorism The base of the nose is broad and sunken in. The eyebrows are not grown together. The corneae are clear (slit-lamp examination). No megalocorneae The distantia pupillae is increased The large and broad tongue hangs out of the mouth. The lips are thick The teeth are small and far apart The colour of the face is pale. The ears are coarse. The girl has a low voice.
Heart and lungs are normal. The liver and spleen are slightly enlarged. There is a small umbilical hernia The abdominal wall is thick. On the extremities some impetiginous spots are seen Acrocyanosis, malformation of the hands and anomalies of the nails are not present.

Neuro-psychiatric Examination: (Age 4 years 2 months)

The motor functions of the cranial nerves are normal. Patient says a few words, but these are barely audible. There is strong motoric restlessness. Patient makes grimaces The musculature is normally developed. The muscular power is good Fascicular contractions are not noticeable The sensibility seems not to be disturbed There is no ataxia in walking or standing The grasping movements are well coordinated There are no tremors Spontaneous nystagmus is absent. The optokinetic nystagmus is normal The pupils are middle wide and react well to light and convergence
The oculopalpebral reflex is not increased The cornea-, masseter and pharynx reflex



Fig 24
Case XIV, girl N, age 4 yrs 2 mths

is normal The abdominal reflexes are low The periost reflexes of arms and legs are lively The Trommer reflex is negative There is inclination of extension of the big toe by eliciting the foot-sole reflex Cloni cannot be elicited
The muscle tone is normal The cog-wheel phenomenon is absent Smell and taste sensations cannot exactly be examined Patient reacts to visual and auditory stimuli On caloric vestibular stimulation no reaction is seen of the left labyrinth The right labyrinth shows a long latency period and a short nystagmus duration
The examination of the intellectual functions is made difficult by the negativistic and

gained
, seems
notion
of her surroundings and her own body At times she is very reserved, laughs into space and stares upwards At times there is a noticeable somnolence The development of speech is retarded Patient does not react to oral instructions She can only fulfil a task after it has been shown a few times The imprint here seems to be slow When contacting strangers, the patient is negativistic, suspicious and anxious She is very attached to her parents The mood is to a high degree dependant on factors in her surroundings She easily flies into tantrums
There are manifestations which point to an increased oral libido Patient continually sucks her fingers, and frequently puts articles in her mouth She also delights in throwing things away, but not until she has touched them with her mouth The appetite is good. The sleep rhythm is quite disturbed The facial expression is fixed On physical examination the patient is not cooperative

Electro encephalographic examination

The E.E.G contained too many bilateral synchronous theta and delta activity, especially in the occipital regions The sleep record was normal The E.E.G was classified as a type pointing to diffuse cerebral disturbances



Fig 25 Strong vascular impressions Shoe-shaped sella

X Ray findings

Skull (Fig 25) The wall of the skull is of normal thickness Strong vascular impressions The sutures are open. The frontal bone is prominent The shoe-shaped sella is not enlarged The pneumatisation of the mastoids is scanty

skull. The forehead is prominent The hair on the head is thick, stiff and shiny There is hypertelorism The base of the nose is broad and sunken in. The eyebrows are not grown together The corneae are clear (slit-lamp examination) No megalocorneae. The distantia pupillae is increased The large and broad tongue hangs out of the mouth. The lips are thick. The teeth are small and far apart The colour of the face is pale. The ears are coarse The girl has a low voice

Heart and lungs are normal The liver and spleen are slightly enlarged. There is a small umbilical hernia The abdominal wall is thick On the extremities some impetiginous spots are seen Acrocyanosis, malformation of the hands and anomalies of the nails are not present.

Neuro-psychiatric Examination: (Age 4 years 2 months)

The motor functions of the cranial nerves are normal Patient says a few words, but these are barely audible There is strong motoric restlessness. Patient makes grimaces The musculature is normally developed The muscular power is good Fascicular contractions are not noticeable. The sensibility seems not to be disturbed There is no ataxia in walking or standing The grasping movements are well coordinated There are no tremors Spontaneous nystagmus is absent The optokinetic nystagmus is normal. The pupils are middle wide and react well to light and convergence.

The oculopalpebral reflex is not increased The cornea-, masseter and pharynx reflex



Fig 24
Case XIV, girl N, age 4 yrs 2 mths.

is normal The abdominal reflexes are low The periost reflexes of arms and legs are lively The Trommer reflex is negative There is inclination of extension of the big toe by eliciting the foot-sole reflex Cloni cannot be elicited

The muscle tone is normal The cog-wheel phenomenon is absent Smell and taste sensations cannot exactly be examined Patient reacts to visual and auditory stimuli On caloric vestibular stimulation no reaction is seen of the left labyrinth The right labyrinth shows a long latency period and a short nystagmus duration

The examination of the intellectual functions is made difficult by the negativistic and

Patient could walk at the age of 14 months
Speech development was clearly delayed At the age of 2 years he was clean.

FIRST EXAMINATION: (Age 6 years 3 months)

The facial expression has gargoyle features The hair on the head is thick The forehead is not prominent. The ears are large. The eye-brows are grown together. There is hypertelorism The root of the nose is sunken in. The small teeth are far apart Some rudiments are missing Macroglossia is not observed The colour of the face is pale The cheeks are chubby.
The structure and clearness of the cornea is normal (slit-lamp examination).
The neck is broad and short Heart and lungs are normal
B.P. 110/80 Broad thorax with chicken-breast and Harrison's grooves The liver is slightly palpable The spleen cannot be felt. Thick panniculus adiposis. The abdomen is prominent There is no umbilical hernia. The penis is normal. The right testicle is not descended (it is present in the inguinal canal) The left testicle is not to be found (neither in the scrotum nor the groin).
The skin is slightly oedematous There are many large and small café au lait spots to be seen on the trunk. The back and extensor sides of the arms are hairy
No acrocyanosis The hands are noticeably large and broad The fingers are relatively short and broad The nails are normal The little fingers are radially curved.
The vertebral column shows no scoliosis or kyphosis The lumbar lordosis is not flattened In the hip and knee joint there is a slight flexion contracture

Neuro-psychiatric examination (Age 6 years 3 months):

The motor functions of the cranial nerves are intact The speech is slow. The patient sometimes stutters The muscles are normally developed. The muscle power is good No fascicular contractions are observed The movements are slow While walking, normal accompanying movements of the arms are noticed. There is no motoric restlessness The sensory functions are intact in every way. There is no ataxia while standing or walking The grip-movements are well co-ordinated There are no tremors Romberg's test is negative Normal finger to nose test as well as that of knee and heel Spontaneous nystagmus *is absent.* The optokinetic nystagmus is normal The pupils are of medium width, equal in size and react well to light and convergence The oculopalpebral reflex is not increased
The corneal-, masseter and pharynx reflexes are normal The abdominal and cremaster reflexes are lively The arm reflexes are normal and the periost reflexes of the legs lively It is possible to elicit some ankle cloni on both sides On evoking the foot-sole reflex the inclination to extend the big too is seen on both sides The muscle tone is normal The cog-wheel phenomenon is absent. The smell and taste sensations are not disturbed The visus is bad, owing to hypermetropy on both sides The audiogram is normal The caloric vestibular examination shows an equal reaction on both sides, but the irritability seems to be somewhat lower than usual
On examination of the intellectual functions, the impression is gained that there is a retarding of development.
The imprint is slow Speech development appears to be partially disturbed The patient speaks with a few words and never makes a complete sentence. It is not possible to get him to repeat short sentences The naming of articles and pictures of objects is fairly good He has difficulty in spontaneously finding the correct name For example, he says tea instead of tea-pot. However, he does know to give a definition how to use these objects Vocabulary and knowledge of numbers are more or less even to the norm applied to this age The achievements, according to past history data, have gradually improved It was noticed motoricity remained slow His disposition is friendly He is not anxious



Fig. 26
Fishhook-shaped vertebral bodies
Tongue-like projections
Microspondylia of L 4 and 5

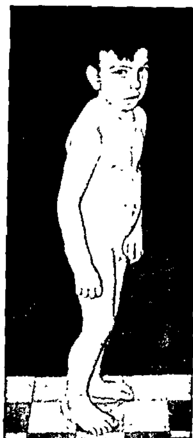


Fig 27
Case XV, boy O, age 6 yrs 3 mths

Thorax Barrel-shaped thorax Hefty clacivles, especially the sternal portion The ribs are broad and run a horizontal course The ends of the lowest ribs are narrowed, like a paint brush

Vertebral column (Fig 26) The vertebral bodies are "fish-hook" shaped in the thoracolumbar transition area There is an arcuate kyphosis at the level of Th 10/11 Th 11 is clearly flatter than Th 10 and Th 12 Th 11 shows a tongue-like projection to the fore, in the middle of the vertebral body The vertebral body of L 4 and L 5 is small

Hands The first and second phalanges are cone-shaped There is a pseudoepiphysis at the distal end of metacarpal I The metacarpals are fairly plump

Pelvis The pelvis is broad and flat The acetabuli are well shaped The neck of the femur is far too thick and erect Pronounced coxae valgae

CASE XV

BOY O· Fig 27

CASE HISTORY.

Patient is the fifth of five children

A brother died as the result of pneumonia (7½ years) and a small brother died 2 days after birth (icterus) The mother is very nervous

The birth of the patient took a long time Patient had often colds and suffered repeatedly from infectious diseases

The motions are mostly fairly hard A tonsillectomy was done

level of his development can be called normal in so far as intellectual functions are concerned The patient has remained definitely slow in his thoughts, imprint, reaction and action

CASE XVI

GIRL P, Fig 29 and 30

CASE HISTORY.

Patient is the third of three children. The birth was normal A first cousin died 17 hours after birth, as a result of fibroelastosis of the myocardium of the left ventricle.

[illegible] (Age 2 years 1 month) [illegible] The [illegible] ound [illegible] is heard [illegible] sunken in

The eyebrows are not grown together The fundus is normal on both sides. The corneae are spotted by tiny flakes on both sides in all layers, at the periphery a little more than central The tongue is broad The normally shaped teeth are somewhat too far apart. The tonsils are large and purulent.



Fig 29
Case XVI, girl P, age 3 yrs

The neck is short and broad. The thorax is broad Her breathing is stertorous Shape of the heart and heart sounds are normal. The abdomen is broad Liver and spleen are not palpable No umbilical hernia The abdominal wall is thickened The buttocks show erythro squamous lesions as the result of monilia infection. The skin of the head, lower arms and legs is dry and scaly There is also some oedema of the skin The child can stand if it is supported There is a pronounced thoracolumbar scoliosis of the vertebral column No kyphosis

The hands are short and broad as well as the fingers

The appetite and sleep are good Patient is clean The spontaneous activity is small Patient only plays when he is forced to do so. He is passive, slow and apathetic. He has a decisive visual interest. The psychomotorism is poor The patient gives every assistance when physically examined.

Electro-encephalographic examination:

The alpha rhyth was rather slow and to much intermingled with slower components Intermittent series were present of theta waves especially in parietal areas, to the right somewhat stronger than to the left, increasing during hyperventilation The E E G indicates moderate diffuse disturbances, with the maximum in deeper structures, to the right more than to the left

X-Ray findings:

Skull The skull is noticeably high and broad The roof of the skull is fairly thin Increased impressiones digitatae The sella is normal Pneumatisation of the mastoids is also normal.

Thorax· Strong ribs and clavicles Barrel-shaped thorax

Pelvis The pelvis is high and narrow Coxae valgae The acetabulae are normally shaped Plump metaphyses of the femur

Vertebral column· Broad lumbar vertebrae L 2 and L 3 are fish-hook shaped

Hands. Broad and short fingers The first and second phalanges are cone-shaped On the right there are 7 and on the left 6 hand-root nuclei visible Broad and plump metacarpals

Feet (Fig 28) Very broad metatarsal bone I The epiphysis of the 1st phalanx digit II and III shows a wedge-shaped distal limitation

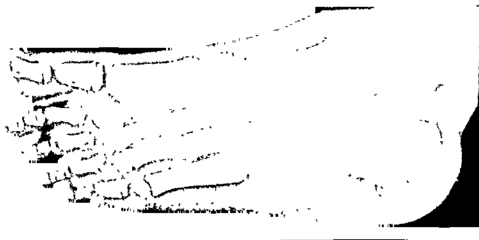


Fig 28 Broad metatarsal I
Wedge-shaped epiphysis of the 1st phalanx digit II and III

SECOND EXAMINATION: (Age 7 years 2 months)

Since the correction of his visus (spectacles, resp + 3 and + 4), the efficiency of the patient has reasonably improved He now follows elementary school The speech is still slow He sometimes stutters Patient can copy sentences and spontaneously makes well-formed sentences He now correctly names objects The efficiency in arithmetics is comparable with that of the norm at his age He draws badly The

psychomotility is poor On examination the behaviour is negativistic, but not anxious

Electro-encephalographic examination

With closed eyes there was an alpha rhythm with normal frequency in series substituted by activity of half the frequency

Diffusely there was too much theta-activity During sleep there was a.o. a pronounced beta-activity in series, to the left stronger than the right, up to 80 micro V. The described findings point to asymmetric disturbances of deep structures.

X-Ray findings

Skull (Fig 31). Thin skull wall Noticeably short, high and broad skull The large fontanel is open. The sutures are open The sella-entrance is widened

Vertebral column Thoracolumbar scoliosis Open arch of S 1; L 1 and L 2 have a concave limitation at the front.

Pelvis Coxae valgae

Hands The shape of the hand is broad and short. The skeleton shows no abnormalities

Thorax The thorax is broad The course of the ribs is horizontal



Fig 31 Large fontanel widely open
Widened sella entranee

SECOND EXAMINATION (Age 3 years).

The face has now suspect gargoyle features The large fontanel is still open. The face has become fatter The teeth show no abnormalities The colour of the cheeks is slightly red The nails are not malformed

The speech is limited to murmur sounds There is still motoric restlessness, patient

Neuro-psychiatric Examination: (Age 2 years 1 month)

The motor functions of the cranial nerves seem to be intact. The muscles are normally developed. There is motoric restlessness.

The sensory functions cannot exactly be judged. Cerebellar function disturbances are absent. The pupils are middle wide and react well to light. The oculopalpebral reflex is increased and the reflexogenous area thereof is extended to the back of the head. The masseter reflex is lively. Normal corneal reflex.

The pharynx reflex is weak. The periost reflexes of the arms are lively. Normal abdominal skin reflexes. The periost reflexes of the legs are normal. In eliciting the foot-sole reflex, inclination to extend the large toe is seen on both sides.



Fig. 30
Case XVI, girl P, age 3 yrs

The tone of the muscle is normal. The smell and taste cannot be determined. The patient reacts well on light stimuli. She does not react to sound stimuli on the right, but does so on the left.

On caloric vestibular examination, the long latency period and the short nystagmus duration give the impression that irritability is diminished (right stronger than left). The intellectual functions show a retardness in development. The obtained level is about the same which is to be expected in a normal development at the age of 8 months. Speech is not yet developed. Only murmur sounds are produced. Patient makes continual movements with the hands, but scarcely moves the legs. Only now and then she sits down, but she cannot maintain this for any length of time. She can drink by herself, but has to be helped with food.

Her affectivity is disturbed. It is not possible to make the patient laugh. She does not seek social contact, neither with the person who looks after her, nor with the children in her vicinity. She is not tiresome.

Her mood is quiet. Her instinctive behaviour is weakly developed. She likes to make sounds by means of toys and laughs when the expected sound is heard. The

Fig 32 Case XVII, boy Q, age 4 yrs 6 mths







Fig 33 Case XVII, boy Q, age 4 yrs 6 mths

makes rhythmic rolling movements of the trunk. Further she gnashes her teeth a great deal There are slight choreiform movements
arms, but signs of scratching cannot be seen.
Patient can stand with aid and walk a few steps.
She mostly lays on her back with her legs elevated, like a baby. In gripmovements, sometimes a slight tremor of the hands is noticed. There is no nystagmus The masseter reflex is lively and the pharynx reflex is low. The oculopalpebral reflex is strongly positive
In percussing the perioral area, no spasm of the muscles of the face is noticed
The periost reflexes of the arms are lively. The reflex of Trommer is bilaterally positive The abdominal reflexes are weakly positive. The periost reflexes of the legs are normal. Cloni cannot be elicited. In evoking the foot-sole reflex on both sides, extension of the large toe is observed
Patient shows still no interest in other children around her
She often puts her thumb in her mouth and then makes sucking movements She sleeps conspiciously a great deal

CASE XVII

BOY Q Illus Fig 32 and 33 *

CASE HISTORY:

Patient is the youngest of two children The brother is healthy. At the birth — which was spontaneous and on time — the patient was noted to have large ears. The weight at birth was 3500 gram.
Patient was operated for an anal fistula at the age of 6 months He had often colds and otitis media, he also had a tonsillectomy done
The closure of the fontanels was delayed Patient was late in walking, he was clean from 3½ years

EXAMINATION: (Age 4½ years).

The facial expression is typical of that of gargoylism The skull is noticeable long and broad The hair on the head is bristly The forehead is prominent The colour of the cheeks is pale. The broad nasal root is sunken in The eyebrows are grown together. The ears are large The small teeth are too far apart His voice is shrill The lips are thick Hair is visible on the upper lip The tongue is not enlarged. On eye-examination no corneal cloudiness is found The neck is short and broad No cardiovascular abnormalities On auscultation bronchitic sounds are heard There is a small umbilical hernia The liver is enlarged The spleen is not felt The hands and fingers are broad and thick The fingers are curved Moreover the little finger is radially curved The nails are short There is increased hair growth on the back and the extensor sides of the extremities The skin of the right thigh shows a few "café au lait" spots

Neuro-psychiatric examination (age 4½ yrs)

The motor functions of the cranial nerves are intact The speech is not disturbed
Normal developed musculature The muscle power is normal Fascicular contractions are absent. Motoric restlessness is noticeable
The movements are unwieldy and stiff
As the result of this, the patient has a cumbersome and heavy walk During walking, normal accompanying movements of the arms are seen
No sensory disturbances can be detected

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* We thank Dr J M. J Tans that he gave us the opportunity to examine this patient

BOY R Fig 34 and 35.

CASE HISTORY:

Patient is the eldest of two children The sister is healthy. The mother noticed that during pregnancy she felt little movement of the child On the photo of the pelvis — which was taken shortly prior to the birth of the patient — the position of the child was normal. The head, however, was enlarged. The birth was terminated by means of forceps extraction The weight at birth was 4420 grams At birth a large swelling, due to the confinement, was noticed at the back of the head, as well as bruises on the forehead, as the result of the forceps extraction The breathing commenced immediately.

On medical inspection immediately after birth, besides the enlarged head, there was also seen an under-development of the external genitals

On the X-Ray photos — made a few days after birth — a shoe-shaped *sella* was visible

During the first few months of life, the development did not worry the parents.

Gradually, however, it became obvious that there was a retardedness of the motoric development and that the circumference of the skull had increased *in an alarming* manner



Fig. 34. Case XVIII, boy R, age 8 mths

FIRST EXAMINATION (Age 8 months)

There is a cracked pot sound The *head* is noticeably long The fore-head is prominent. The large fontanel is wide *open* The hair on the head is light and soft The ears are not enlarged The eye-*brows* are grown together above a sunken nose-bridge There is hypertelorism [illegible]
The first tooth is visible An o[illegible]
strabismus convergens With s[illegible]
The neck is short and broad Heart and lungs are found to be normal. [illegible] is seen
There is no umbilical *hernia*. The liver is enlarged The spleen is not palpable There

There is no ataxy when walking or standing The grip movements are well coordinated. Spontaneous nystagmus is absent while optokinetic nystagmus can be evoked in both directions. The pupils are middle wide, equal in size and react well to light and convergence The oculopalpebral reflex is lively, but pathologically not clearly increased The cornea-, masseter and pharynx reflex are normally elicited. The arm reflexes ar lively. The abdominal and cremaster reflexes are positive The reflexes of the legs are normal The muscle tone is not increased The cog-wheel phenomenon is absent Patient reacts well to light and sound stimuli.

The intellectual functions are retarded. The general level is that of debility The imprint is slow and perseveration is noted The vocabulary and the language he uses shows only a small retardness as compared with the norm for the age. The patient has difficulty in concentration and shows lack of perseverance.

The mood is friendly and anxious There is little liveliness when contacting the patient For this age there exists a too strong desire to be in contact with his mother. In the instinctive behaviour the patient shows definite shortcomings.

He is fond of music Further, he likes to colour pictures and does simple puzzles Now and then he sucks his fingers without it being conspicious in his behaviour He does not allow anything to be taken away from him and becomes aggressive if he does not get his own way He has tantrums He soon tires on exertion. His appetite and sleep are undisturbed The psychomotility is hardly differentiated

Spinal fluid. The liquor is normal in pressure and composition

The flocculoreaction of proteins (mastix, gold and benzoic acid) shows a normal curve

Electro-encephalographic examination.

With closed eyes there was an alpha-rhythm of 7-9 per sec., mixed with theta and delta components, persistant with eye opening Photic-stimulation induced some occipital following (alpha frequencies) The EEG was classified as to be abnormal, pointing to slight disturbances in deep structures

Joints

There is a hunching of the shoulders

The lordosis of the lumbar vertebral column is increased The pronation and supination of the lower arms show a clear restriction All movements of the extremities are limited Genua valga

X-Ray findings.

Skull The roof of the skull has a normal thickness The frontal bone is prominent The lambdoid and parieto-temporal sutures are open Rather strong vascular impressions The sella is enlarged and shoe-shaped The entrance of the sella is widened The mastoids contain little air

Thorax Hefty clavicles (specially at the sternal end) Broad ribs, running practically in a horizontal direction The 4 lowest ribs are oar-shaped The outline of the heart is normal The thorax is barrel-shaped

Vertebral column The lowest and upper limitation of the vertebrae in the thoracal area are convex The intervertebral discs are narrow. The frontal limitation of the vertebral body of Th 2 to inclusive Th 8 is concave The frontal limitation of Th 9 to inclusive L 3 is characterised by the protrusion of the centre part of the vertebral body

Pelvis No anomalies are noticed

Hands The first and second phalanges are cone-shaped Coarse trabeculations of the diaphysis of the metacarpals and phalanges The proximal ends of the metacarpals are irregular in shape Four ossified carpal centres are visible

Feet These shows similar findings but less extensive

BOY R. Fig 34 and 35

CASE HISTORY:

Patient is the eldest of two children. The sister is healthy. The mother noticed that during pregnancy she felt little movement of the child On the photo of the pelvis — which was taken shortly prior to the birth of the patient — the position of the child was normal The head, however, was enlarged The birth was terminated by means of forceps extraction The weight at birth was 4420 grams At birth a large swelling, due to the confinement, was noticed at the back of the head, as well as bruises on the forehead, as the result of the forceps extraction. The breathing commenced immediately

On medical inspection immediately after birth, besides the enlarged head, there was also seen an under-development of the external genitals.

On the X-Ray photos — made a few days after birth — a shoe-shaped sella was visible

During the first few months of life, the development did not worry the parents

Gradually, however, it became obvious that there was a retardedness of the motoric development and that the circumference of the skull had increased in an alarming manner



Fig 34 Case XVIII, boy R, age 8 mths

FIRST EXAMINATION (Age 8 months)

There is a cracked pot sound The head is noticeably long The fore-head is prominent The large fontanel is wide open The hair on the head is light and soft The ears are not enlarged The eye brows are grown together above a sunken nose-bridge There is hypertelorism On inspection of the mouth no anomalies are observed The first tooth is visible An optic atrophy is found on both sides There is periodic strabismus convergens With slit-lamp examination no corneal cloudiness is seen The neck is short and broad Heart and lungs are found to be normal. There is no umbilical hernia The liver is enlarged The spleen is not palpable There

is hypogenitalism The penis is conspicuously small. A small hard testis is felt on both sides in the scrotum The hands and feet are short and broad. The nails are normally shaped The hair-growth is normal The feet are slightly red

Neuro-psychiatric examination: (Age 8 months).

The motor functions of the cranial nerves are intact, apart from the already mentioned periodic strabismus convergens, which must be attributed to the diminished visus The child murmurs



Fig 35 Case XVIII, boy R, age 8 mths

The muscles are normally developed, and the power of same is not disturbed The spontaneous motoric activity is noticeably small Only movements of the arms are noticed, but there are practically no movements of the legs The head can turn but cannot be raised The child cannot turn himself, and is not able to sit The sensory functions seem to be intact The grip movements betray no ataxia There are no tremors Spontaneous nystagmus is absent, while optokinetic nystagmus can be evoked in both directions

The pupils are middle-wide, equal in size and react well to light The menace-reflex is not increased The oculopalpebral reflex is clearly increased, and the reflexogenous area thereof is extended The corneal, masseter- and pharynxreflexes are normal The reflexes of the extremities are normal Bilaterally the Babinski reflex can be evoked, which is normal for the age The abdominal and cremaster reflexes are positive Cloni cannot be elicited The muscle tone is normal The cog-wheel phenomenon is absent

Smell and taste cannot exactly be determined The vision is disturbed as the result of a double-sided optic atrophy There is good reaction to sound stimuli

In caloric vestibular stimulation a long latency period is observed on both sides The nystagmus duration is shorter on the left than on the right side

The development of the intellectual functions is retarded The retardation is also clear in respect of the motor functions and instinctive behaviour This is more noticeable when the mood is rather lively There is little spontaneous interest The affectivity shows no noticeable disturbances

The appetite and sleep are not disturbed The child has no difficult character. The emotional expression shows an adequate differentiation.

Electro-encephalographic examination

There was an alpha equivalent rhythm with a normal frequency with high amplitudes Diffusely theta-activity was noted Also the sleep record was marked by high amplitudes On photic-stimulation little following was seen The E.E.G. was classified as to be diffusely disturbed, to a slight extent, as the result of disturbances mainly of deep structures

Joints There are no contractures

X-Ray findings

Skull Thin skull wall The frontal bone is prominent The large fontanel is wide open The skull sutures are open, except the coronary sutures The sella is shoe-shaped The mastoids contain little air The angle of the jaw is noticeably blunt

Thorax Hefty curved clavicles Hefty ribs have a horizontal course. Barrel-shaped thorax

Vertebral column Flattened lumbar lordosis

Pelvis Coxae valgae Broad iliac bones

Hands Brachyphalangia of the metacarpal I There is one ossified carpal centre visible

SECOND EXAMINATION (Age 1 yr)

The large fontanel is still wide open

The face has become broader and the cheeks fatter. The colour of the cheeks is bright red The teeth present, (four above and two below) are angular and far apart. The liver is somewhat more enlarged than at the previous examination

On neurological examination, apart from the double-sided optic atrophy and a too lively oculopalpebral reflex, it is now noticed that the child moves his arms and legs less than before

Cloni cannot be evoked

The pupils react to light Sitting is still not possible He puts articles, presented to him, into his mouth The appetite is excessive There is a preference for certain foods The mood is apathetic and the demeanour passive

Chapter V

POST MORTEM AND BIOPSY REPORTS

A POST MORTEM REPORTS

The reports are the result of a close co-operation with several pathologists
The following review precedes the description of the available data

Report No	Pathologist	Clinical case-* report	Sex	Age	Post Mortem
1	Wyers H J G and Slooff J L	XIII	F	1 yr	19 hrs after death
2	Botman Th and Tans J M J	VI	M	2 yrs 9 mths	30 „ „ „
3	Schillings P. H M	X	F	6 yrs 6 mths	60 „ „ „
4	Botman Th	VII	M	7 yrs 5 mths	31 „ „ „
5	Kramer W	XI	F	12 yrs	6 „ „ „

* The Roman figures refer to the clinical case reports in Chapter IV

1 POST MORTEM OF A FEMALE CHILD AGE 1 YEAR

Height 67 cm Well nourished High forehead, large cranial vault The lobes are completely adherent The eyebrows are continuous above the somewhat sunken-in nasal bridge. The tongue is normal in size The neck is very short Under the jaw, in both axillae and both groins small lymph glands are felt
No icterus, cyanosis or abnormal pigmentation
External genitals normal
On opening up, the liver seems considerably enlarged and lies in the medioclavicular line about 3 fingers below the arch of the ribs Spleen and stomach are not visible. There is no large omentum present No free fluid in the abdomen In the right pleural cavity 54 cc clear yellow fluid is present, while in the left pleural cavity only 5 cc The lungs collapse moderately The thymus appears smaller than one would expect. The thyroid is normal in size and shape The heart is slightly enlarged The apex is formed by the left ventricle The epicardium is smooth throughout The cavities of the heart are not widened *The foramen ovale is closed The mitral, tricuspid and* pulmonary valves are completely normal The papillary muscles and trabeculi are normal The endocardium is sound, except for about ½ cm below the aortic valves where the endocard is clearly thickened and grey of colour with canary-yellow spots The aortic valves are also grey and clearly thickened, and somewhat rigid so that they

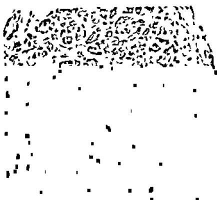


Fig 36

Heart muscle Vacuolisation of many muscle fibres

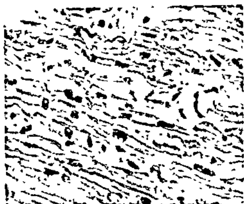


Fig 37

Heart muscle Vacuolisation of the fibres especially next to the nuclei Between some fibres large cells with vacuolar protoplasm and small dark nucleus

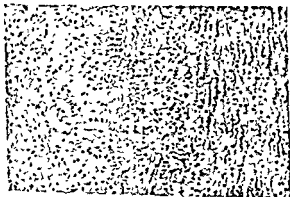


Fig 38.

Aorta To the left media, to the right greatly thickened intima, containing many large cells.

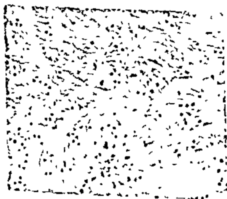


Fig 39

Aorta Thickened intima Many large cells with vacuolar protoplasm

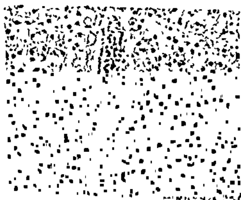


Fig 40

Liver Intense vacuolisation of liver cells, especially around the triangle of Kiernan A few large cells at the edges of these triangles, the nature of which is not clear

Chapter V

POST MORTEM AND BIOPSY REPORTS

A. POST MORTEM REPORTS

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Height 67 cm Well nourished High forehead, large cranial vault The lobes are completely adherent. The eyebrows are continuous above the somewhat sunken-in nasal bridge The tongue is normal in size The neck is very short Under the jaw, in both axillae and both groins small lymph glands are felt
No icterus, cyanosis or abnormal pigmentation
External genitals normal
On opening up, the liver seems considerably enlarged and lies in the medioclavicular line about 3 fingers below the arch of the ribs Spleen and stomach are not visible. There is no large omentum present No free fluid in the abdomen In the right pleural cavity 54 cc. clear yellow fluid is present, while in the left pleural cavity only 5 cc The lungs collapse moderately The thymus appears smaller than one would expect The thyroid is normal in size and shape The heart is slightly enlarged The apex is formed by the left ventricle The epicardium is smooth throughout The cavities of the heart are not widened The foramen ovale is closed The mitral, tricuspid and pulmonary valves are completely normal The papillary muscles and trabeculi are normal The endocardium is sound, except for about ½ cm below the aortic valves where the endocard is clearly thickened and grey of colour with canary-yellow spots The aortic valves are also grey and clearly thickened, and somewhat rigid so that they

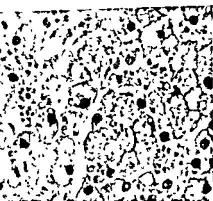


Fig 41

Liver Vacuolisation of the liver cells; to the left some large vacuolised cells, the nature of which is not clear

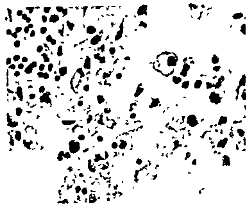


Fig 42

Lymph gland Desquamated swollen and vacuolised cells in the medullary sinus

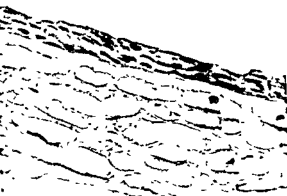


Fig 43

Cornea Epithelium intact Bowman's membrane not impaired Oedematous substantia propria



Fig 44

Spinal cord Anterior horn cells Hyaline and vacuolar swelling of the protoplasm Tigroid-substance often marginally displaced

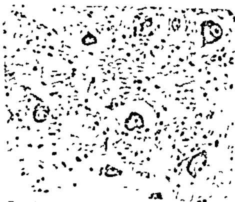


Fig 45

Spinal cord Clarke's column Fairly normal aspect

do not collapse. The beginning of the aorta is thickened and resistant on cutting The inside shows the same spotty canary-yellow markings. The descending aorta, also the abdominal part, seems thickened but shows no yellow spots The lungs show a smooth pleura. There are marked differences in consistency and colour, on cutting, both lungs show several pink and yellow-pink, somewhat granular, foci Along the main bronchi and at the bifurcation there are various swollen lymph glands In the mesentery many fairly large lymph glands are seen, on cutting some are found to be pink, others canary-yellow The liver is enlarged (weight 450 grams) The surface is smooth, spotty, varying from brown-red to yellow
The spleen is somewhat larger than normal (weight 35 grams), and shows normal follicular and trabecular markings The vertebral column has a straight course; the physiological curves are totally absent. On opening the skull, adherence of the dura to the skull is seen, neither skull nor brains show macroscopical anomalies
In completing the postmortem no anomalies or special features are seen in the other organs

Microscopical examination.

*The heart (Fig 36 and 37) shows slight interstitial oedema wherein exudate cells and mast-cells are also found In the outer margins of the adventitia of the myo-*cardial vessels, here and there fairly large cells are seen with vacuolar protoplasm Everywhere the endocardium is fairly thick, and contains some empty vacuoles In this thickened endocardium some large cells are also found, similar to those in the adventitia of the vessels In the large epicardial vessels a rather noticeably broadening of the intima is found, with an increase of connective tissue, oedema and some large cells with vacuolar protoplasm
With Sudan III and P A S staining there is neither in the vacuoles of the connective tissue nor of the large cells Sudan positive or P A S positive material present The sections through the aorta show a definite thickened intima (Fig 38 and 39), whereby interstices and cavities between the fibrous structures are seen which either show a foamy structure or appear to be empty
With various Sudan-technics no Sudan-positive material is seen There is no double refraction visible and also with osmic-acid no blackstaining can be obtained Sporadically a small amount of glycogen (P A S) is present The structure of the liver is seen to be normal The central veins are somewhat widened and the portal spaces probably have more connective tissue than normal The liver cells (Fig 40 and 41) show fairly strong vacuolisation, sometimes foamy and sometimes coarse The Kupffer star-cells are also swollen and slightly vacuolar In the liver cells and also in the Kupffer star-cells a slight amount of glycogen is found (P A S-staining with and without ptyaline)
With Sudan III and Sudan-black very little fat is found in the liver cells, and neither the P A S-staining nor the fatstainings give sufficient explanation about the contents of the vacuoles in the liver and Kupffer cells
With polarised light no double refraction in the frozen sections can be demonstrated
The kidneys are very decomposed Probably there are no important anomalies excepting swelling and vacuolisation of the tubulus epithelia, probably especially of the tubuli contorti II
The spleen shows nothing abnormal The lymph-glands (Fig 42) show lymphoid-tissue with relatively few cells, and a slight increase of the reticular-cells, of which a few show a somewhat vacuolised protoplasm
The lungs show multiple bronchopheumonic foci with desquamation of many alveolar epithelia The sections through the cornea (Fig 43) show no anomalies of Bowman's membrane There is no increase of cells or nuclei The lamellae of the substantia propria are pressed aside greatly through oedema, neither in the P A S-staining nor

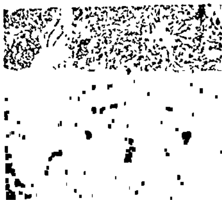


Fig 46

Spinal cord Anterior horn cells Osmium tetroxyde Slight osmium-positive substance in the ganglion cells

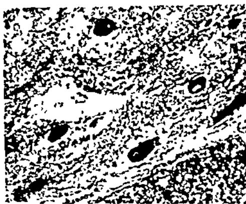


Fig 47.

Spinal cord Clarke's column Intense black-staining with osmium tetroxyde



Fig 49

Brain Enlarged part of Fig 48 In the adventitia some large cells with vacuolar protoplasm.



Fig 48

Brain Widened Virchow Robin space Perivascular increase of cells

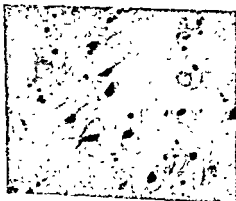


Fig 50

Brain (Feyrter) Swollen and somewhat vacuolised ganglion cells with displacement of the nucleus towards the periphery

with Sudan, are substances found in the vacuoles capable of taking these stains

Spinal cord·

The upper part of the spinal cord is examined in two levels They show approximately the same picture, although the anomalies in the lower situated sections are clearer than the higher ones. The anterior horn cells (Fig 44) are clearly swollen and show accumulation of a granular somewhat brown material in the protoplasm, whereby the nucleus and the tigroid-substance is pressed to one side.
The tigroid-substance is crumbled.
Other cells show a more equal glassy structure of a portion of the protoplasm and show pictures which somewhat resemble the so-called "Primare Reizung" (Primary irritation). The large cells of Clarke's column show the anomalies in a lesser degree (Fig. 45). Moreover here the pictures of a primary irritation are normal The Azan-staining colours the granular substances in the ganglion-cells somewhat pink In the anterior horn cells stained with Sudan III only slight orange colouring is found With P A S staining, nowhere pink or red colouring is seen.
In the anterior horn cells, when stained with osmic-acid, only a few small black granules or globules are seen (Fig 46) The cells of Clarke's column and those of the posterior horn are stained intensely black (Fig 47)

Brains

Sections are made of the brain from the frontal lobe, the motoric zone, the occipital lobe and the basal ganglia In all sections a clear broadened Virchow-Robin space is seen (Fig 48 and 49)
The ganglion cells of the motoric area are swollen and rounded in places There is a slight pyknosis of the nucleus and the nucleolus is hardly visible (Fig 50 and 51) In other sections similar anomalies are seen in some nerve cells, but in a lesser degree In P A S staining many ganglion cells appear to take on a somewhat pink colour, especially in the occipital area, but definitely not more intense than the normal ganglion cells do In Sudan-staining of the paraffin sections slight orange colouring of the nerve cells is found in the occipital area

Summary

As cause of death the disseminated bronchopneumoniae are considered Further, there is a peculiar thickening of the aorta valve and the endocardium below The intima *of the aorta is also abnormally thickened Further there is a vacuolar abnormality* in the liver cells and in many reticuloendothelial system cells About the contents of these cells, no opinion could be obtained A number of spinal cord cells show degenerative anomalies *In the brain cells also some anomalies are seen, which* however are less clear

2 POST MORTEM OF A MALE CHILD AGE 2 YEARS 9 MONTHS

Height 82 cm

Well fed The large forehead projects to the front Large skull roof The large fontanel is not entirely closed The teeth are quite normal The neck is fairly short The chest is flat and broad In both groins some small lymph glands are felt On opening up, the liver appears to lie 3 cm below the arch of the ribs The spleen reaches up to the arch of the ribs There is no free fluid in the abdomen
The thymus weighs 10 grams The heart is normal The intima of the aorta and of the pulmonary artery is sound The liver (715 grams) and the spleen (45 grams) are enlarged The weight of the brain is 1300 grams The pituitary body is not enlarged. The lateral ventricles of the brain are not obviously widened The fourth

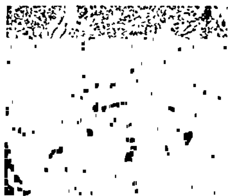


Fig 46

Spinal cord Anterior horn cells Osmium tetroxyde Slight osmium-positive substance in the ganglion cells

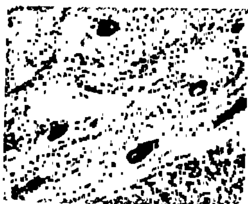


Fig 47.

Spinal cord Clarke's column Intense black-staining with osmium tetroxyde.

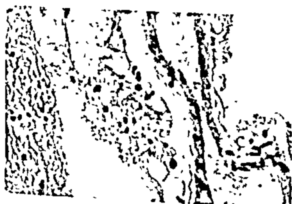


Fig 49

Brain Enlarged part of Fig 48 In the adventitia some large cells with vacuolar protoplasm



Fig 48

Brain Widened Virchow-Robin space Perivascular increase of cells

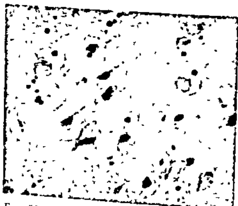


Fig 50

Brain (Feyrter) Swollen and somewhat vacuolised ganglion cells with displacement of the nucleus towards the periphery

ventricle and the aquaeduct are normal. On section of the lowest third part of the putamen a cystic space is present measuring 7x12 mm. In the complete post mortem, no anomalies or special features are seen in the other organs

Microscopical examination:

The examination of the heart shows no abnormalities The liver cells are large and contain vacuolar protoplasm. The evenly-shaped nuclei are mostly situated peripherally. The Best-staining is weakly positive. With Sudan very little or no fat is visible
The kidneys show no important anomalies, apart from vacuolisation of the protoplasm of tubulus epithelia, especially of the tubuli contorti.
The Sudan staining is negative, There are no double refracting crystals visible
In the lungs bronchopneumonic foci are found

Spinal cord:
All ganglion cells are swollen, especially the anterior horn cells and the cells of Clarke. (Fig 52 and 53)
The nucleus and tigroid substance are pressed to the periphery The nucleus is sometimes curved inwards
The protoplasm is minutely granular The changes are most pronounced in the anterior horn cells
Cochlear and vestibular ganglion (Fig 51)
The ganglion cells are swollen. The protoplasm is granular vacuolar The nuclei are partially pyknotic and mostly pressed towards the periphery

Brains

a Horizontal section through the right temporal lobe and internal capsule (Paraffin material).

In Kluver-staining the marrow shows, in some places, diffuse pallor, besides this the Virchow-Robin spaces around the vessels are greatly thickened
In the cortex many ganglion cells contain in the protoplasm granular material, which takes on a slight colour with fat-staining substances This is particularly noticeable in the 3rd and in a lesser degree in the 5th and 6th cortical layer, but in no layer these pathological cells are absent It is striking that in deeper cortex layer both completely normal cells are found and pathological ones
In the dentate gyrus the ganglion cells contain relatively less pathological material, on the other hand in the hippocampus gyrus large quantities
The pathological material in the protoplasm of the ganglion cells when stained with Kluver turns blue, with haematoxyline-eosine however, it is only very slightly coloured (pink) *In P A S staining it is only slightly positive, in the cresyl-violet* no staining takes place, while in the Bodian-staining dirty black granules in the protoplasm are seen There is no sign of glia-reaction in the cortex

b Sagittal section through the right temporal lobe (Paraffin and frozen material)

In this section also in Woelcke and Kluver stainings a diffuse demyelinisation is encountered as well as many very widened Virchow-Robin spaces The largest amount of pathological material is found in the ganglion cells in the 3rd layer Practically all cells in this layer are affected In the other layers there are still normal cells Whether there is a diminishing of ganglion cells is not possible to judge through the increase of volume of the cells With Kluver staining the material turns blue, nearly black with Woelcke-staining, and in the nile-blue sulphate colouring it is a dirty-blue With haematoxyline-eosine staining it is barely coloured (pink), it is only weak P.A.S positive (with and without ptyaline) and it does not stain with

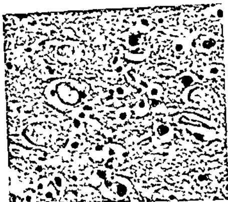


Fig 51
Brain Swollen and vacuolised ganglion cells with flattening and displacement of the nucleus towards the periphery

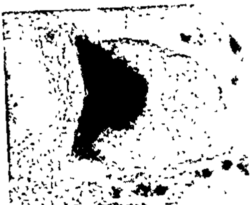


Fig 52
Spinal cord: Clarke's column Swelling of the protoplasm Nuclear displacement

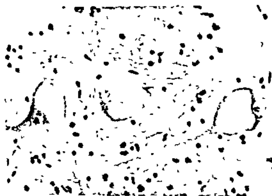


Fig 53
Spinal cord Clarke's column Swelling of the protoplasm Nuclear displacement

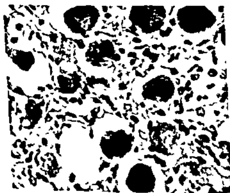


Fig 54
Cochlear ganglion A group of ganglion cells with granular vacuolar protoplasm Pyknotic nuclei

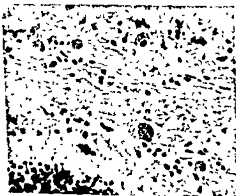


Fig 55
Retina Swollen cells in the ganglion-cell layer with displacement of the nuclei

cresyl-violet. In scarlet-red and Sudan-black staining it is weak positive, in Bodian-preparation in the protoplasm of the ganglion cells light-black granules are seen In frozen sections, with Sudan-black, Sudan III or scarlet-red pathological material is stained weakly positive, and definitely not stronger than in equivalent paraffin sections In the cortex every trace of glia-reaction is absent.

Pituitary body:

Mainly eosinophil and chromophobe cells are found
The basophil cells are definitely in the minority.

3 POST MORTEM OF A FEMALE CHILD AGED 6 YEARS 6 MONTHS

Height 101 cm.

The corpse is already very decomposed The child is moderately fed The head is greatly deformed and the forehead is very prominent Great cloudiness of the corneae does not allow further inspection of the eyes. In the pleural cavity bloody fluid is present. The valves of the heart are all somewhat thickened but otherwise are well moveable. The chordae tendineae are plump. The myocardium is discoloured in a spotty yellow. The intima of the pulmonary artery and aorta are greatly haemorrhagically imbued Numerous yellow discoloured somewhat elevated spots are seen The lungs show macroscopically nothing abnormal. The abdominal organs show autolytic changes
In cutting the meninges some turbid liquor appears. The leptomeninges are strongly oedematous and look turbid There is a striking enlargement of the cerebrum, of which the gyri are broadened and the sulci flattened On section the ventricles are strongly dilated The thickness of the wall of the hemispheres is very reduced.
The pituitary is normal in size The microscopical examination is made difficult through autolysis
The most important finding seems an atheromatosis, as well in small as in large circulation, a strong steatosis of the liver, while the anomalies of the lungs (aspiration pneumonia) can possibly be considered a direct cause of death.
The origin of the hydrocephalus is attributed to a thickening of the meninges
In the retina (Fig 55) foam-cells are found in the layer of ganglion cells

4 POST MORTEM OF A MALE CHILD AGE 7 YEARS 5 MONTHS

Height 119 cm

Well fed Large skull roof The neck is short and broad The chest is flat and broad
There is no swelling of the lymph-glands
The intima of the aorta and pulmonary artery is sound The liver weighs 1360 grams and the thymus 30 grams On examination of the heart it is found to be normal The spleen (220 grams) is enlarged The vertebral colomn shows definite protrusion of the intervertebral discs In opening the skull the sutures are seen to be ossified, except the crown suture, which is syndesmotically closed In the middle skull sulcus, *below the foramina* rotunda et ovalia, elevations are seen which are normally absent The leptomeninges are turbid and thickened
The brain-weight is 1455 grams On section the cerebrum shows an equally widened ventricular system The pituitary body is enlarged (weight 0,825 gram) In the complete post mortem no anomalies of any importance are seen in the other organs

Microscopical Examination.

The heart is quite normal The liver cells are enlarged and show vacuolisation of



Fig. 56
Retina Swollen ganglion cell with displacement of the nucleus and vacuolar protoplasm Pyknotic nucleus

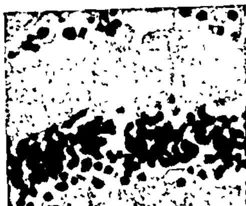


Fig 57
Retina Swollen ganglion cell



Fig 58
Petrous bone Enchondral bone with globuli interossei

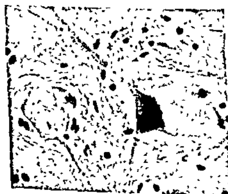


Fig 59
Spinal cord Anterior horn cells Swollen ganglion cells with slight vacuolisation of the protoplasm and displacement of the nucleus Swollen dendrons

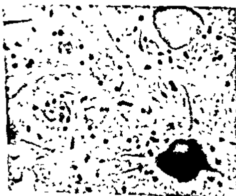


Fig 60
Spinal cord Anterior horn cells Swollen ganglion cells with displacement of the nucleus

cresyl-violet In scarlet-red and Sudan-black staining it is weak positive, in Bodian-preparation in the protoplasm of the ganglion cells light-black granules are seen In frozen sections, with Sudan-black, Sudan III or scarlet-red pathological material is stained weakly positive, and definitely not stronger than in equivalent paraffin sections In the cortex every trace of glia-reaction is absent

Pituitary body:

Mainly eosinophil and chromophobe cells are found
The basophil cells are definitely in the minority

3. POST MORTEM OF A FEMALE CHILD AGED 6 YEARS 6 MONTHS

Height 101 cm

The corpse is already very decomposed. The child is moderately fed. The head is greatly deformed and the forehead is very prominent Great cloudiness of the corneae does not allow further inspection of the eyes. In the pleural cavity bloody fluid is present. The valves of the heart are all somewhat thickened but otherwise are well moveable The chordae tendineae are plump The myocardium is discoloured in a spotty yellow The intima of the pulmonary artery and aorta are greatly haemorrhagically imbued. Numerous yellow discoloured somewhat elevated spots are seen The lungs show macroscopically nothing abnormal The abdominal organs show autolytic changes

In cutting the meninges some turbid liquor appears. The leptomeninges are strongly oedematous and look turbid. There is a striking enlargement of the cerebrum, of which the gyri are broadened and the sulci flattened On section the ventricles are strongly dilated The thickness of the wall of the hemispheres is very reduced.

The pituitary is normal in size The microscopical examination is made difficult through autolysis.

The most important finding seems an atheromatosis, as well in small as in large circulation, a strong steatosis of the liver, while the anomalies of the lungs (aspiration pneumonia) can possibly be considered a direct cause of death

The origin of the hydrocephalus is attributed to a thickening of the meninges

In the retina (Fig 55) foam-cells are found in the layer of ganglion cells

4 POST MORTEM OF A MALE CHILD AGE 7 YEARS 5 MONTHS

Height 119 cm

Well fed Large skull roof The neck is short and broad The chest is flat and broad There is no swelling of the lymph-glands

The intima of the aorta and pulmonary artery is sound The liver weighs 1360 grams and the thymus 30 grams On examination of the heart it is found to be normal. The spleen (220 grams) is enlarged The vertebral colomn shows definite protrusion of the intervertebral discs In opening the skull the sutures are seen to be ossified, except the crown suture, which is syndesmotically closed In the middle skull sulcus, below the foramina rotunda et ovalia, elevations are seen which are normally absent. The leptomeninges are turbid and thickened

The brain-weight is 1455 grams On section the cerebrum shows an equally widened ventricular system. The pituitary body is enlarged (weight 0,825 gram) In the complete post mortem no anomalies of any importance are seen in the other organs

Microscopical Examination:

The heart is quite normal The liver cells are enlarged and show vacuolisation of



Fig 56

Retina Swollen ganglion cell with displacement of the nucleus and vacuolar protoplasm Pyknotic nucleus

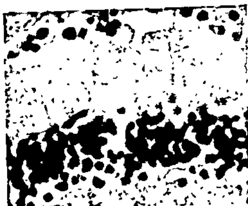


Fig 57.

Retina Swollen ganglion cell.



Fig 58

Petrous bone Enchondral bone with globuli interossei

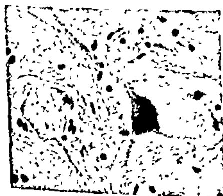


Fig 59

Spinal cord Anterior horn cells. Swollen ganglion cells with slight vacuolisation of the protoplasm and displacement of the nucleus Swollen dendrons

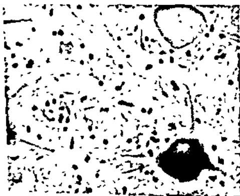


Fig 60

Spinal cord Anterior horn cells Swollen ganglion cells with displacement of the nucleus

the protoplasm. The nuclei are regularly shaped and lie mostly peripherally. The Kupffer star-cells are also swollen and have a vacuolar protoplasm The Best, Sudan and scarlet-red staining give no clear positive result, neither in the lead acetate, aethanol or formaline fixed preparation, nor in the non-fixed preparation, which was kept in deep-freeze The staining with toluidine-blue is clearly positive
On applying this staining method after the action of hyason or after diastasis, no colouring of the preparation was observed
In the lymphatic structure of the spleen, some cells with vacuolar contents are seen The lungs show bronchopneumonic foci. In the retina — specially in the area of entry of the optic nerve — wide-spread, large, swollen ganglion cells are found with vacuolisation of the protoplasm and eccentric, sometimes pyknotic nuclei (Fig 56 and 57) In the other structures of the eye, namely in Bowman's membrane, no anomalies are found.

Petrous portion of the temple bone

The enchondral ossification presents an aspect as shown in Fig 58

Spinal cord (Fig 59 and 60)

Distinct swelling of the anterior horn cells The protoplasm is granular vacuolar. The nucleus and the tigroid are pressed to the periphery The nucleus is sometimes curved inwards The Clarke-cells show these changes in a minor degree

Cochlear and vestibular ganglion.

The ganglion cells are swollen The nuclei are partially pyknotic and pressed to the periphery The protoplasm is granular-vacuolar. The anomalies in the larger cells of the vestibular ganglion are far less obvious than in the smaller ones (Fig 61, 62 and 63)

Cerebrum

Sections were made of the brain, namely of the motor area of the cortex In the sections most of the ganglion cells appear to be swollen. The protoplasm is granular-vacuolar, and the nuclei lie mostly peripherally. With the P A S staining the ganglion cells appear to be P A S positive With the Sudan-staining the ganglion cells are stained light-orange The Virchow-Robin spaces are widened

Pituitary Body

The anterior lobe is obviously enlarged There is colloid-accumulation in the acini Only a few basophil cells are seen Some eosinophil cells are multi-nuclear.

5 POST MORTEM OF A FEMALE CHILD AGED 12 YEARS

Height 102 cm

The general condition of the body shows under-nourishment In the lungs emphysema of the lower lobes is found It is difficult to dissect all the organs as they are too tough The heart muscle is coloured yellow and tough of consistency There is much coagulated blood in the heart, part of which is removed for laboratory examination The liver is greatly enlarged and has an uneven surface (weight 750 grams) The pancreas is large and has a yellow colour
Skull section The largest circumference is 64 cm. The roof of the skull is paper thin and the dura markedly thickened The sinuses are passable The brain convolutions are broad and the grooves flattened There is turbidity and thickening of the arachnoids In removing the brains ± 1550 cc liquor is collected The weight of the brains is 1250 grams.
On cutting strongly dilated ventricles are found The wall of the hemispheres is reduced to a membrane of only 1½ cm thickness Numerous small cysts are found

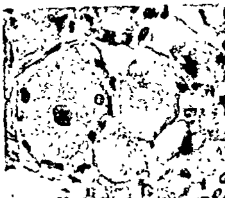


Fig 61

Vestibular ganglion A group of large ganglion cells with slight granulation and many small vacuoles in the protoplasm



Fig 62.

Vestibular ganglion A group of large ganglion cells with uneven stained protoplasm



Fig 63.

Vestibular ganglion A group of small cells with numerous vacuoles of nearly even size Nuclei are partly pyknotic



Fig 64

Brain Amorphous substances in globular-shaped swollen ganglion cells, the structure of which is lost Next to them, some ganglion cells with amorphous substances in the cytoplasm, only a sporadic axon process [illegible]

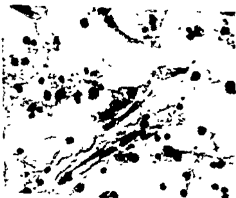


Fig 65

Nasal polyp Around the blood vessel some large cells with granular vacuolar protoplasm To the right a detached cell

the protoplasm The nuclei are regularly shaped and lie mostly peripherally. The Kupffer star-cells are also swollen and have a vacuolar protoplasm The Best, Sudan and *scarlet-red staining give no clear positive result, neither in the lead* acetate, aethanol or formaline fixed preparation, nor in the non-fixed preparation, which was kept in deep-freeze. The staining with toluidine-blue is clearly positive
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On cutting strongly dilated ventricles are found The wall of the hemispheres is reduced to a membrane of only 1½ cm thickness Numerous small cysts are found

With P.A.S.staining (Fig 65) this same material reacts positive. In the sections treated with ptyaline this substance is hardly less stained than without With Sudan-black the granules in the cells react positive In consequence of the fact that the substance found in the large cells of the polyp, reacts positive to Sudan, Sudan black and P.A S stains, it is concluded that these cells possibly contain a substance, probably a glycolipid (ganglioside?)
In the polyp also some Russel-bodies are seen, which is not surprising considering the number of plasma-cells

Summary
Oedematous, inflamed nasal-mucous membrane polyp, with large macrophages, which contain a ganglioside-like substance

2 LIVER (CASE X)

In the sections the liver-cells appear to be slightly swollen and contain a great deal of glycogen (P.A S staining) The glycogen is evenly distributed over the liver-trabeculi Apart from the glycogen the liver-cells contain another substance, because they are somewhat vacuolar, but in the vacuoles no substances are found which take on the P A S, Sudan III or Sudan-black stains Conspicuous are some large cells with small dark nuclei and with sharply circumscribed protoplasm, which shows a somewhat streakly light vacuolar character These cells lie especially in and around the Kiernan's *triangles* They are considered to be cells which have accumulated some kind of substance Neither the cells, nor their localisation are typical enough to define them *in more detail* With Azan-stainings, the protoplasm in the cells stains a bright blue The reticulin-stainings do not give a further discernment.

3 LYMPH-GLAND

In the sections through the lymph-gland, a proliferation of reticulo-endothelia is found, of subcapsular and medullary sinus
Also in the medullary sinus a number of large cells are seen of the same type as those of the large cells around the Kiernan's triangles

in the white as well as in the grey matter. The floor of the third ventricle is very thin and to a certain extent ventrally distended The aquaeduct is very wide and as far as can be investigated, the foramen of Magendi is wide open It seems possible that in the posterior skull groove a cyst was present at the distal side of the cerebellum, which has pressed the vermis and tonsils dorsally and the medulla oblongata ventrally.

Microscopical examination:

The pia mater is somewhat thickened due to the increase of connective tissue fibrils and cells. The cortex of the hemispheres has become very narrow, and lamination is lost. The number of blood-vessels has greatly increased and the space of Virchow-Robin around the blood-vessels greatly enlarged

There is a definite marginal sclerosis. In the ganglion cells (Fig 64), as well as in the glia-cells an amorphous substance is present, whereby these cells have been blown up to a balloon-shape while the nucleus has been pressed to the edge. Sometimes round masses of an amorphous substance are noticed, in which cell structures no longer can be recognised Not only the neurones but also the glia-cells contain this amorphous mass. There are numerous hazy ganglion cells The number of glia-cells is greatly increased The myelin substance has been completely lost and replaced by a glia-network with numerous fibrillous astrocytes Some U-fibres are maintained On the border of the white and grey matter numerous microcysts are present, which, as far as can be gathered, have developed from peri-vascular spaces There is an intense proliferation of the periadventitious cells of the blood vessels In the wall of the blood vessels a homogeneous substance is seen

In places signs of an ependymitis granularis are observed Not only in the grey matter of the brain, but also in the cerebellum, cells are noticed loaded with amorphous substances, surrounded by degenerated tissue products Everywhere the white matter is atrophic.

In the pons it is noticed that the tegmentum is narrow, while the base has normal proportions.

Summary

Great destruction of the grey and white matter of the C N S caused by the deposition of amorphous substances in the cells

As a result of this the white as well as the grey matter is to the greater part lost, while a compensatory hyperplasia of the glia-cells has developed No certain explanation is found for the enormous hydrocephalus, but probably this is the result of a cyst situated in the cisterna magna

Not only in the central nervous system accumulation products are found, but also these are found in spinal ganglia, pancreas, liver, spleen, lungs, heart, kidneys, ovaries, aorta, thymus and cartilage

The accumulation products, in as well as outside the central nervous system, are stained in a large measure with P A S staining and with Sudan staining

B BIOPSY REPORTS

1 NASAL POLYP (CASE IX)

The polyp consists of oedematous connective tissue with a fairly thick infiltration of plasma-cells, lymphocytes and granulocytes It is covered with normal ciliated pseudostratified columnar epithelium In the stroma, apart from the cells mentioned, some cells are seen with vacuolar, barely stained protoplasm and small nucleus

In the paraffin-sections of formaline-fixed tissue stained with Sudan, in a number of these large cells, granular matter is seen which has a light brownish-red colour

As far as could be established the patients described gave evidence of insufficient development of their mental powers during the first three years of their lives. There are, therefore, no patients with a so-called "late" form of gargoylism, in which only after the third year of life clinical signs become manifest

Most of them started walking late. In the majority of cases speech development was disturbed Usually between 3-6 yrs. a mental deterioration was noticed in the more severe cases.

Further, the anamnestic data are in conformity with the opinion, reflected in the literature, that gargoylism is a conditioning factor for the acquiring of pneumonia, bronchitis, pharyngitis, rhinitis, tonsillitus, otitis media and other chronic or recurrent affections of the respiratory tract

B BIOMETRIC DATA

The data referring to height, weight and skull circumference are summarized in the following table, arranged according to the age of the patient:

Case	Sex	Age yrs	Age mths	Height in cm	Height (In comparison with the normal age standard)*	Weight In Kg	Weight (In comparison with the normal standard) Height	Weight (In comparison with the normal standard) Age)*	Circumference of skull In Cm	Circumference of skull (In comparison with the normal age standard)*	Skull Length/width in cm
XIII	F	0	6	63	— 4,5%	5,68	—13,9%	—23 %	41	— 6,7%	
XVIII	F	0	8	71	+ 1,3%	10,9	+26,7%	+28,2%	54,6	+19 %	19 /14
XVIII	F	1	0	78	+ 4,1%	12	+16,5%	+23,7%	56,5	+19,7%	19 /14,5
XII	F	1	2	77	+ 1,7%	11	+11,1%	+15 %	47	+ 6,6%	
VIII	F	1	5	80	— 1,2%	13,6	+24,8%	+23,6%	53	+ 9 %	17 /15
XVI	F	2	1	82	— 3,3%	11,04	+ 0,4%	— 5,1%	50	+ 3,5%	15 /14
X	F	2	6	94	+ 5,6%	15,2	+ 9,3%	+20,6%	57	+16,8%	
VI	F	2	9	82	—11,5%				52	+ 4 %	17,5/15
XVI	F	3	0	88	— 5,6%	14	+15,7%	+ 3,7%	51,8	+ 5,1%	15 /14
II	M	3	3	97	+ 0,5%	18,8	+25,1%	+25,3%	57	+12,8%	
XIV	M	4	2	96	— 5,5%	16,5	+14,6%	+ 4,4%	52	+ 4 %	
XVII	M	4	6						56,5	+ 9,5%	
III	M	5	5	119	+ 6,7%	30	+37,6%	+57,9%	55	+ 6,6%	19 /13
V	M	5	6	108	— 3,2%	26,4	+48 %	+39,7%	53	+ 2,3%	16 /15
IX	M	5	9	93	—16,7%	16,3	+21,3%	—12 %			
X	M	5	10	101	— 9,7%	22,5	+48 %	+20,3%	59,5	+15,5%	20 /15
XV	M	6	3	123	+ 6,4%	26	+11,5%	+27,5%	52	— 1,3%	17 /15
I	M	6	10	108	— 8,8%				56	+ 7,3%	19 /15
VII	M	7	4	119	— 2,9%	28	+28,9%	+22,3%	60	+14,1%	20 /16,5
IV	M	8	2	113	—10,9%	27	+39,2%	+12,5%	53	+ 0,8%	16 /15
III	M	8	3	123	— 2,6%	32,5	+39,5%	+32,1%	58	+13 %	19 /15
V	M	9	0	118	—11 %	27,5	+28,5%	+ 0,7%	55	+ 3,6%	17,5/15
IV	M	11	0	117	—16,5%	33	+57,8%	+ 1,8%	54,5	+ 1,7%	16 /16
XI	M	11	9	102	—29,6%				62	+16,5%	21 /16

* Calculated according to the tables in the Textbook of Endocrinology by R H Williams M D

Chapter VI

SUMMARY AND DISCUSSION OF THE CLINICAL DATA DESCRIBED IN CHAPTER IV

A PAST HISTORY

1. Consanguinity

No consanguinity was found in the parents of the patients described before Perhaps this is related to the fact that in at least six (Case I up to and including VI) and possibly even in eleven (Cases VII, VIII, XV, XVII, XVIII) of the eighteen patients the disease is sex-linked.

2 Familial incidence

The familial incidence is most obvious in Cases I to VI inclusive. The patients described are all boys, belonging to one ancestry, wherein the disease appeared at least in fourteen persons. The second family with multiple cases is represented by Cases VII and VIII; these patients are brothers A third family where a multiple incidence is found, is represented by Case IX A brother of this patient is possibly also a gargoyle patient

3. Heredity

In Cases I to VI inclusive, there is a recessive-X-chromosomal inheritance (see ancestry Fig. 1)

In Case IX recessive autosomal inheritance may be presumed because a brother of this female patient probably also suffers from gargoylism

In the remaining patients it is not clear whether the condition is homozygous or heterozygous Neither is it clear whether there are patients in which the disease must be attributed to a gene mutation

4. Pre-natal peculiarities

Perhaps it is worthwhile mentioning that the mother of one patient (Case XVII) during pregnancy observed abnormally little foetal movement In this patient, after the birth, there was definite motor inertia

5. Birth

In 8 of the 18 patients the birth was abnormal (long duration of labour, Caesarian section or forceps extraction). In three of the eight patients an abnormally large skull was noticed at birth.

Case	Contractures	Umbilical hernia	Hair anamolies	Teeth anamolies	Macroglossia
I	+	+	+		+
II		+	+		
III	+	+	—	+	+
IV	+		+	+	+
V	+	—	+	+	—
VI	+				—
VII		+	+	+	+
VIII	+	+	+	+	—
IX		+	+	+	+
X	+	+	+	+	+
XI	+	+	+	+	+
XII	+	+	+	—	—
XIII	+	—	+		—
XIV	+	+	+	+	+
XV	+	—	+	+	—
XVI	+	—	—	+	—
XVII	+	+	+	+	—
XVIII	—	—	—		—

The numerous café au lait spots mentioned in case XV are of interest in connection with a publication of NÖLLER [106], in which a patient is described with both gargoylism and skin fibromata. SALAM and ZELLWEGER [306, 213] described a family with a case of gargoylism as well as one of Recklinghausen's disease. Further, it is of interest to note the presence of leukonychia in Cases IV, V and VII.

D EYE EXAMINATION

Summary

Case	Sex	Corneal Cloudiness	Slit lamp examination performed	Optic-atrophy	Special Features
I	M	—	no	—	
II	M	weak +	no	—	
III	M	—	yes	—	
IV	M	—	yes	—	
V	M	—	yes	—	
VI	M	—	no	—	
VII	M	—	yes	—	
VIII	M	—	yes	—	
IX	F	+		+	
X	F	+		?	
XI	F	+	no	?	
XII	F	—	yes	—	
XIII	F	+	yes	—	
XIV	F	—	yes	—	
XV	M	—	yes	—	hypermetropy
XVI	F	+	yes	—	
XVII	M	—	yes	—	
XVIII	M	—	yes	+	

From this survey it is obvious that the height is below the normal age standard. Marked degrees of retardation in growth are conspicuous in the higher age group.
These data support the opinion of ZELLWEGER et al[307] that there is a progressive retardation of growth with increasing age.
The body-weight usually exceeds the normal standard for age and height. The circumference of the skull is usually greater than is normal according to age. In general it may be said that the moderately enlarged skulls are brachycephalic and the greatly enlarged skulls mesocephalic.

C FACIAL EXPRESSION AND HABITUS

Practically all patients had the Hurler-facies to a greater or lesser extent The facial expression typical of gargoylism became increasingly obvious with age. To the description given in the literature we may add that the face of many of the patients is reminiscent of someone with a bad cold, about to sneeze. The grin of short duration, which precedes sneezing, appears constantly on the face of the gargoyle patient, giving it a stark and painful expression. A clown-like expression also occurs (see Fig 7)
The resemblance between the intrafamilial cases, as described in the first six cases, was striking. However, the facial expression in Case IV was different from that of the other patients. In some patients the cheeks were bright red, but in others this phenomenon was lacking Moreover, it was noticed that the bright red colour disappears during the course of the disease (Case V). However much the patients resembled each other on account of their facial expression, there was a still greater resemblance in their habitus. Generally speaking they could be considered as pyknic. The relatively large head, the short, broad neck, the flat broad thorax, the fat abdomen, the plump broad hands and fingers lend the general appearance of the gargoyle patient an aspect that is even more characteristic of the disease than the facial expression because, in our opinion, it is neither dependent on the phase of the disease, nor on the age of the patient Another typical aspect, dependent on the age of the patient and the phase of the disease, is the posture of the patient when standing and walking, viz., the flattened lumbar lordosis, sometimes accompanied by a thoracolumbar kyphosis, and the flexion contracture position of the legs, at the hip and knee joints and the often present genua valga.
We shall not go more deeply into details noticed on inspection, such as contractures, skin and hair anomalies, the occurrence of an umbilical hernia, teeth, tongue and nail anomalies Suffice it to give a broad survey of the appearance of some of these anomalies

The heart in two patients was definitely abnormal, suggestive of a congenital anomaly. In these cases the blood pressure of the femoral arteries was too low, while in another patient there was a definite hypertension. On electrocardiographic examination, no abnormalities were registered. In some patients a systolic murmur was detected above the base of the heart, and in one an enlargement of the heart to the left. Diffuse glandular enlargement was observed in one case only. Most patients suffered from a chronic coryza. According to McKUSICK[274] and MURRAY[319] the mobility of the thorax is diminished in a large number of patients. Although our case histories included no data pertaining to this feature, it is reasonable to assume that a diminished mobility existed on account of the broad and flat shape of the thorax and the horizontal course of the ribs in the majority of our patients. It should be mentioned here that in two cases microgenitalism was present, while in other patients the external genitals were well developed. A large number of laboratory tests have been carried out on most of the patients, including the determination of sodium, potassium, chloride, phosphorus, urea, cholesterol, acid and alkaline phosphatase and the copper content of the blood. Further, the protein spectrum of the blood was determined by means of paper-electrophoresis. Apart from determining the fasting blood sugar level in many cases a glucose tolerance-curve was also made. Liver function tests were carried out.

The urine was examined chromatographically by means of paper-electrophoresis for the presence of amino-acids. In some cases the hormone content of the urine was estimated. Blood and urine examination was routine in all cases. Apart from this, slides were made of the peripheral blood-picture, to demonstrate the anomaly of Reilly (Giemsa-Wright staining). This *anomaly*, however, was not found in any of our *patients*.

The sternal punctate was examined in cases IX, X and XIII.

In Case X there was an increase in reticular cells, a spongy *structure of the* protoplasm and a large, sometimes eccentric and flattened *nucleus*.

The basal metabolism could only be examined in the few cooperative patients.

The following values were found

Case X B.M — 3,6 *resp.* — *10; resp.* — *14*

Case XV B M + 12

In case X tracer investigation with I^{131} *gave remarkable* results because this substance was almost entirely retained by the *thyroid*

Hormone excretion via the urine (mg. *per 24 hours*).

Case	IV	IX	X	XIII	XV	XVIII
17-ketosteroids	1,4	0,3	6,9	0,3	2,3	*1,0*
17-hydroxycorticosteroids			0,0		14,9	5,6
Gonadotropic hormones			15 U		5 *U*	
Oestrogenic hormones					7 U	

Optic atrophy was diagnosed in two patients (Cases IX and XVIII). On account of pronounced corneal cloudiness, it was impossible to examine oculi in Cases X and XI.

A "cherry-red macula", which may occur in amaurotic idiocy, was not noticed in any of the patients. The corneal cloudiness in Case II is noteworthy, because this was a case of sex-linked heredity. According to the literature corneal cloudiness is not seen in sex-linked cases. Delayed pupil widening with mydriatics was observed in Cases VII and XIII. This phenomenon is repeatedly mentioned in the literature [31, 60, 71]. The importance of detecting errors of refraction is obvious from Case XV, in which a hypermetropia was diagnosed. After correction of vision there was an obvious improvement in his achievements at school.

E COCHLEAR AND VESTIBULAR FUNCTIONS

The results of the investigations are represented in the following summary

Case	Age	Reactions to sound stimuli	Reaction to caloric stimulation	Impression of the sensitiveness of the labyrinth, judged by nystagmus duration and latency period
XIII	0, 6	+	+	diminished
XVIII	0, 8	+	+	diminished, left more than right
XII	1, 2	+	+	diminished
VIII	1, 5	+	+	diminished
XVI	2, 1	Right — Left +	+	diminished, right more than left
XIV	4, 2	+	Left — Right +	left abolished right diminished
III	5, 5	+	—	abolished
V	5, 6	+	—	abolished
X	5,10	+	—	abolished
XV	6, 3	Normal audiogram	+	slightly diminished
VII	7, 4	+	—	abolished
IV	8, 2	+	—	abolished

It is important to note that in cases with mental deficiency, it was practically impossible to accurately establish the auditory disturbances The impression gained from the patients was that there was a gradually decreasing reaction to sound stimuli, which of course does not imply either that the organs of hearing did, or did not, function normally From the summary the impression is gained that in most cases there is a diminishing sensitiveness of the labyrinth during the course of the disease

F MEDICAL AND ENDOCRINE ANOMALIES AND LABORATORY FINDINGS

As in cases reported in the literature, a hepatosplenomegaly was found in most of our patients. Intestinal disorders, seldom mentioned in the literature, were also seldom encountered in our patients.

The heart in two patients was definitely abnormal, suggestive of a congenital anomaly. In these cases the blood pressure of the femoral arteries was too low, while in another patient there was a definite hypertension. On electrocardiographic examination, no abnormalities were registered. In some patients a systolic murmur was detected above the base of the heart, and in one an enlargement of the heart to the left. Diffuse glandular enlargement was observed in one case only. Most patients suffered from a chronic coryza. According to McKUSICK[274] and MURRAY[339] the mobility of the thorax is diminished in a large number of patients Although our case histories included no data pertaining to this feature, it is reasonable to assume that a diminished mobility existed on account of the broad and flat shape of the thorax and the horizontal course of the ribs in the majority of our patients It should be mentioned here that in two cases microgenitalism was present, while in other patients the external genitals were well developed. A large number of laboratory tests have been carried out on most of the patients, including the determination of sodium, potassium, chloride, phosphorus, urea, cholesterol, acid and alkaline phosphatase and the copper content of the blood. Further, the protein spectrum of the blood was determined by means of paper-electrophoresis Apart from determining the fasting blood sugar level in many cases a glucose tolerance-curve was also made. Liver function tests were carried out. The urine was examined chromatographically by means of paper-electrophoresis for the presence of amino-acids. In some cases the hormone content of the urine was estimated Blood and urine examination was routine in all cases Apart from this, slides were made of the peripheral blood-picture, to demonstrate the anomaly of Reilly (Giemsa-Wright staining) This anomaly, however, was not found in any of our patients.

The sternal punctate was examined in cases IX, X and XIII

In Case X there was an increase in reticular cells, a spongy structure of the protoplasm and a large, sometimes eccentric and flattened nucleus.

The basal metabolism could only be examined in the few cooperative patients.

The following values were found:

Case X B.M — 3,6 resp. — 10, resp — 14.
Case XV B M + 12.

In case X tracer investigation with I[131] gave remarkable results because this substance was almost entirely retained by the thyroid

Hormone excretion via the urine (mg. per 24 hours).

Case	IV	IX	X	XIII	XV	XVIII
17-ketosteroids	1,4	0,3	6,9	0,3	2,3	1,0
17-hydroxycorticosteroids			0,0		14,9	5,6
Gonadotropic hormones			15 U		5 U	
Oestrogenic hormones					7 U	

The usefulness of the laboratory examinations proved to be small when considered in relation to the number carried out. We shall therefore restrict ourselves to a recording of the positive results:

	Cholesterol	P B I	Copper	Alkaline phosphatase	Serum proteins (paper electrophoresis)					Total proteins
					Albumin	Globulin alpha II	alpha I	beta	gamma	
mal ues	130-250 mgr%	4-7 γ%	98-124 γ%	5-15E KA	54-64 rel%	6.2-8 5 rel%	7.8-11.4 rel.%	9 1-13 0 rel.%	12.1-17.6 rel.%	6-8 gr%
se										
II	249									
III		5,8	125	20 17,2	47,1	8,6	15	13,6	15,7	7
IV	292	3,9	196	29	48	5,9	14,3	13,4	18,3	6,7
V	253	4,6	198	28	50,2	7,3	12,8	14,8	15,2	7
VI	196									
/II	140		205	22,5	41,1	9,6	17,8	15,1	16,5	6,9
III	187,5			40,58	60	6,2	13,0	11,5	9,2	6
IX	125				36,6	3,1	8,6	6,7	6,6	6,2
X	380			24,2 35,2						
XI	268			18,5	42,7	7,5	18,5	11,5	19,6	5,3
III	188		163	34	44,9	9,2	19,4	14,3	12,2	6,7
IV	198		131	34	53,2	8,1	11,3	12,9	14,4	6,2
(V	237	6,5		14,9	48,2	8,9	11,6	11,6	19,7	7
VI	237	5,8		17,7	50,5	8,3	14,7	12,7	13,8	6,4
/II				24,2	67,0	2,5	11,5	9,0	10,0	7,9
III	147,7	7,1		14,3	56,7	6,2	12,3	12,9	11,8	6,8

Lipid spectrum of the blood.

	Standard	Case X	Case IX
Tot. amount of lipids	500—900 mg %	1112 mg %	525 mg %
Lipid phosphorus	7—9 mg %	14 mg %	5 5 mg %
Neutral fat	0—400 mg %	360 mg %	262 mg %
Cholesterol	150—280 mg %	380 mg %	125 mg %

From these surveys it appears that hypercholesterolaemia was present in several cases In one of our cases (Case X) practically all fractions of the lipid spectrum of the blood were increased. Similar findings have been described in the literature [271]. In some patients the copper content of the blood-serum was definitely increased, a phenomenon also described in the literature [251] The alkaline phosphatase level in the blood was in most cases moderately raised. In the literature normal levels predominate [20 21 103 141 167 186, 191 197 198 227 250], although in a minority of cases moderately raised levels have been observed ([47 236 283 319]), and only exceptionelly low levels ([141 186]). The protein spectrum (paper-electrophoresis) presented, as a rule, the following features

1. Normal protein content.
2. Decreased albumin/globulin ratio.

3 Increased alpha-2-globulin fraction. (This is in agreement with the findings of LÖWENTHAL[241]).
4 Incidental deviations from the normal levels of the other globulin fractions

Although in various patients signs were observed, suggestive of Cushing's disease, acromegaly and myxoedema, the results of our investigations disproved the presence of these conditions In our cases as in the literature, the endocrinological investigation results vary from case to case. This variability seems understandable, at least to some extent, in gargoylism, for whereas in some cases the pituitary is of normal size, in other cases the adenohypophysis is enlarged and in still another category of patients the pituitary body is reduced in size as result of pressure in the presence of a variable degree of hydrocephalus, which itself can cause hypothalamico-endocrinological disturbances. It seems worthwhile to mention here that the X-Ray picture of the sella does not provide reliable information as to the true size of the pituitary.

G NEUROPSYCHIATRIC DISTURBANCES

In Chapter II it has already been explained how our study of the literature — specially the publication of C. de LANGE and WOLTRING — resulted in a distinction being made between two types, viz., the classic type, where the disease is accompanied by neurolipidosis, and the typus E where this is absent Clinically, it may be remembered, the difference between the two types consists in the presence or absence of psychic or neurological abnormalities For further details reference may be made to Chapter II.
An example of typus E probably does not appear in our own material. Although it is true that there are some cases in which progressive mental deterioration is absent, the other signs of the disease are so slight that it is perhaps more correct to consider these cases abortive. Apart from these latter cases, the anomalies found can be summarized as follows.

I A progressive deterioration process preceded by oligophrenia
II A very slowly progressive neurological condition, resulting in a spastic tetraparesis or tetraplegia and cortical, sub-cortical, striate and brainstem lesions
III. Hydrocephalus, as a rule of a progressive character, in the large majority of cases

Ad I

The oligophrenic development which clinically precedes the deterioration is marked by a progressive retarding in development tempo and by malformation of the personality of the child which leads finally to complete developmental arrest
Only when this has taken place do the signs of a progressive deterioration become conspicuous

The usefulness of the laboratory examinations proved to be small when considered in relation to the number carried out. We shall therefore restrict ourselves to a recording of the positive results:

	Cholesterol	P B I	Copper	Alkaline phosphatase	Serum proteins (paper electrophoresis)					Total protein
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of being angular. As a rule an increase in the oculopalpebral reflex with extension of the reflexogenic zone was detectable, sooner or later. This phenomenon was absent only in the light cases. The further course of the disease was characterized by an increasingly inadequate and imperfect progress of motoric behaviour pattern; the patient usually impressed one as being apractic. This was commonly followed by a slowly progressive spastic diplegia, firstly of the lower and later also of the upper extremities, while, at the same time not only bulbar but also the pseudobulbar phenomena appeared. These included primitive mouth reflexes, deglutition disturbances, depression of the pharynx reflex, increase of the masseter-reflex, a strongly positive facial reflex and an increased reaction to threat. It was often noticed that the mouth contained excessive amounts of saliva and this was attributed to difficulties experienced in swallowing. In one patient insufficient saliva secretion was observed (Case IV)

In the beginning of the illness various patients gave one an impression of suffering enhanced sensations of hunger and thirst.

In the later stages however, it was usual to note a progressive decrease of appetite, as well as pathological increase of desire for sleep

In one patient (Case II) affective loss of tonus was observed. Sensory examination was difficult to carry out efficiently on account of the lack of intellectual power of most of the patients.

It was, however, noticed that many disliked being touched They reacted also to pain stimuli. Definite cerebellar anomalies were not observed. One patient suffered from epileptic fits (Case XI). In two cases there was a bilateral optic-atrophy. In a number of cases examination of the papillae nervi optici was not possible because of corneal cloudings In the most advanced stages of the disease the patient lay practically motionless in bed, with extended arms as well as the legs and with feet in a pointed position Further, it should be remarked that there were no signs of disturbance of the periferal nervous system Electromyographic examination could not be carried out on this group of patients It may be mentioned in passing that the patients showed a gradually decreasing reaction to sound stimuli. In the final stages they did not react at all to vestibular stimuli In some patients, with a slight symptomatology, the abovementioned neurological anomalies could not be detected. It is, however, possible that in such abortive cases these signs will still appear at a later date

The results of electro-encephalographic examination may be summarized as follows *

1. As a rule no constant asymmetries
2. No focal or generalized epileptic activity
3. Generally speaking excessive slow activity.

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* We are grateful to our colleague J Mol, neurologist at Heerlen General Hospital, for his assistance in recording and interpreting the E.E.G tracings

Initial examination revealed, apart from a retardation in the striving after and the acquiring of sensual and intellectual knowledge, a disturbance of temperament, character, vitality and psychomotility, a disturbance, in other words of the complete personality.
Following upon this period of inadequate and progressive retardation in development a stage is finally reached of complete arrest, as already stated. This did not happen simultaneously in all fields, namely in behaviour experience and function; in some patients for example, there was cessation in speech development, while some progress was still being made in other fields of motor development. Most patients started walking late. Progressive deterioration signs generally appeared between the third and sixth year. The patients gave to an increasing degree the impression of being apractic. Pathological deterioration involved the break down of most cerebral functions, with psychiatric as well as neurological manifestations. It was particularly noticeable that, together with the intellectual deterioration, primitive, oral libidinous behaviour patterns came to the fore.
Compared with the behaviour and experiences of normal children of the same age and sex, there not only appeared to exist quantitative differences but also qualitative ones.
In certain of their behaviour patterns and experiences they appeared to be even less differentiated than are normal healthy infants. All in all this may be said to add up to a deficiency in the majority of the specific human qualities. What remained were fragments of behaviour and a completely disordered psychic life based principally at the animal-vegetative and biological-sensitive level. This was accompanied by an increasing disturbance of social contacts
In a few patients with a slighter symptomatology, there was only an oligophrenic personality development. Follow-up will show whether in these cases pathological deterioration will still take place. In one of the abortive cases noticeable improvement took place, as judged by school achievement after an hypermetropy had been corrected.
The majority of the patients was unable to follow infant school training or even that provided in a special school for backward children
Only one patient seemed capable of following the ordinary elementary school course (Case XV).

Ad. II.

On reviewing the whole range of neurological anomalies, one may conclude that a prominent feature was a decreasing tempo in the development of the neuromotor and psychomotor functions resulting in a steady lowering in the level reached. Speech development was nearly always disturbed and this was most pronounced in those patients in whom walking had begun late
In some motor inertia was seen, in others however, there was a noticeable hyperkinetic behaviour, chiefly in the form of primitive rhythmic movements, but also in other forms of motor restlessness, it sometimes having a choreiform character. The movements were typically stiff and gave the impression

The vascular impressions, however were often pronounced.
In the minority of cases the shape of the sella was considered to be normal; usually shoe-shaped and sometimes a ballooned sella was seen In more than half of the cases the sella was enlarged and the sella entrance widened
In most of the cases the pneumatisation of the mastoids was slight.

Thorax

The thorax was broadened in practically all cases, and there were changes in the clavicles and ribs typical of gargoylism.

Vertebral column:

In most of the patients "fish-hook" shaped vertebral bodies were seen in the thoracolumbar region of the vertebral column. Occasionally tongue-like projections were found on the anterior surface of the vertebral bodies.
Some degree of kyphosis was seen in practically all patients
Spondylolysthesis occurred in three cases

Other signs·

Coxae valgae and changes typical of gargoylism in the bones of the hand and to a lesser degree of the foot, were seldom absent.
In Cases I, IV and V the number of ossified carpal centres was below the normal age standard.

4. Sometimes excessive beta-activity.
5. Tendency to respond on photic-stimulation, with higher frequencies than those of the background rhythms, with a pronounced occipital driving.

Ad. III.

In 8 patients an impression could be gained as to the size of the cerebral ventricles by means of pneumo-encephalography in 3 cases and by the examination of post-mortem material in 5 cases.
In 6 of these the ventricular system was dilated to a varying degree:

	Case	Age yrs mths	Circumference of the skull in comparison with the normal age standard	Skull Length/Wight	Brain ventricles	Symbols expressing the degree of dilation
x	XIII	1,0	— 6,7%	?	No dilation	0
x	VI	2,9	+ 4 %	17,5/15	Dubious dilation of sideventricles	±
–	VIII	1,5	+ 9 %	17 /15	Clearly dilated	+
–	V	5,6	+ 2,3%	16 /15	Clearly dilated	+
–	IV	8,2	+ 0,8%	16 /15	Clearly dilated	+
x	VII	7,5	+14,1%	20 /16,5	Strongly dilated	++
x	X	6,5	+15,5%	20 /15	Very strongly dilated	+++
x	XI	12,0	+16,5%	21 /16	Very strongly dilated	+++

x Post mortem
– Encephalography

This survey shows a correlation between the degree of ventricular dilation and cranial enlargement. It is remarkable that the mesocephaly only occurs in cases with a pronounced ventricular dilation (Cases VII, X, XI), contrary to the brachycephaly seen in the other cases.
As appears from the autopsy reports in chapter V, abnormal thickened leptomeninges have been found in these cases In Case XI, moreover it was considered possible that the dilation of the ventricles has been caused by a cyst, situated in the cisterna magna.

II X-RAY FINDINGS

The main findings may be summarized as follows

Skull:

The skull was enlarged in most of the cases, to a varying degree.
The shape of the skull was mesocephalic in some cases, brachycephalic in others. A thin skull roof as well as open sutures were seen in most of the cases.
In minority of the cases the impressiones digitatae were emphasized.

by KLENK, who was the first to discover and define gangliosides[4]. KLENK showed that this glycolipid contains a substance which he called neuraminic acid.
Nowadays it has been established, amongst others by the work of BLIX, that neuraminic acid besides being a constituent of the gangliosides, occurs also in certain mucoproteins.
According to recent publications neuraminic acid has various important biological functions. Besides neuraminic acid gangliosides contain hexosamine. Further components of gangliosides are fatty acids, galactose and sphingosine. Sphingosine was so named by THUDICHUM on account of the problems he said it presented to the enquirer[332]

II. Disturbances of mucoid substances

Before describing these anomalies some remarks may be made.
Of the mucoid substances, the mucopolysaccharides form an ill-defined subdivision.
This is obvious from the introduction given by MORGAN at a congress on the chemistry and biology of mucopolysaccharides in 1958: "It must be admitted that there is no generally accepted definition of a mucopolysaccharide and for that reason, at this stage in the development of the subject, we must be prepared to include a wide range of carbohydrate containing complexes in our discussion"[325].
ROSEMAN gives the following definition
"In general the mucopolysaccharides may be defined as polysaccharides which usually contain hexosamine and are associated with protein, but which can be separated from protein by relatively mild technics"[333].
The anomalies in the mucoid substances present in gargoylism involve the acid mucopolysaccharides. According to KARL MEYER[335], a pioneer in this field, these substances can be subdivided as follows·

1 Polyuronides, to which hyaluronic acid and chondroitin belong.
2 Sulphated polyuronides, to which chondroitin sulphate A, B and C belong as well as heparitin sulphate, also known as heparin monosulphate.
3 Polysulphates of which, up to the present, only the karatosulphates have been identified

BRANTE[209] in 1952, was the first to notice an increased mucopolysaccharide content in most of the tissues and organs of gargoyle patients DORFMAN et al demonstrated an excess of mucopolysaccharides in the urine[301].
KARL MEYER confirmed this and also proved mucopolysaccharides to be present in excess in the brain tissue. He showed the increased mucopolysaccharides to consist principally of two substances· chondroitin sulphate B (ChS-B) and heparitin sulphate According to KARL MEYER[335], in the publication wherein one also finds the results of his investigation of two of the patients described by us in Chapter IV (Case VII and XI), the ratio of ChS-B to heparitin sulphate in the urine is usually 2 · 1. In cases without

Chapter VII

GARGOYLISM FROM THE BIOCHEMICAL POINT OF VIEW

Only in the last decade and thanks to the work of prominent biochemists has it become possible to describe gargoylism in biochemical terms. That obscure points have remained unexplained is not surprising when one recalls that the biochemical processes involved are those dealing with the still poorly understood metabolism of the lipids and mucoid substances

1. Disturbances of lipids:

Before describing these anomalies, some general remarks should be made. In some countries a distinction is made between lipids and lipoids, i.e. between fats and fatty substances

In other the term "lipids" is used to denote both groups and in this meaning it is used here.

The lipids can be defined chemically as an heterogenous group of naturally-occurring substances, characterized by their solubility properties. They are non-soluble in water and soluble in fat-solvents such as benzol, aether, acetone and tetrachlore-carbon

The lipids, can, according to FOLCH, be sub-divided as follows.

1. Simple lipids, comprising the triglycerides and waxes;
2. Conjugate lipids, consisting of a fatty acid, an alcohol and one or several additional groups. This group comprises the various phospholipids (lecithins, cephalins and sphingomyelins), glycolipids (cerebrosides and gangliosides) and sulpholipids (e.g a cerebroside containing sulphuric acid isolated by BLIX from nervous tissue).
3. Derived lipids, "potential" fatty acid compounds, e.g cholesterol and substances derived from the preceding group, e g. sphingosine, higher aldehydes, fatty acids

The anomalies described thus far in gargoylism are mainly of the gangliosides and appear to be of a quantitative nature

In 1951 BRANTE[169] found an increase of gangliosides in the cerebrum of a gargoyle patient.

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bolism of the mucopolysaccharide or of some of its components, or as regards the binding of the mucopolysaccharide to protein, etc."

From this it appears that the gangliosidosis is not an essential, or at least not the most essential aspect of the disease.

IV. *Summary and discussion:*

According to more recent views, the basic defect in gargoylism is supposed to be a disorder of mucopolysaccharide metabolism [209, 334, 335]. An excess of mucopolysaccharides has been demonstrated in the liver, spleen, meninges, urine [209, 257, 276, 298, 327] and also although to a lesser extent, in the brain tissue of patients with gargoylism [335].

The gangliosidosis, affecting principally the nervous system but also, to a lesser degree other tissues and organs [78, 116, 169, 264, 298], has to be considered as non-obligatory and constitutes in this sense a secondary phenomenon. We suspect the gangliosidosis to be absent in typus E, because here there is no cerebral involvement.

It may be important to know whether or not there are differences between the classical types and typus E as to the chemical nature of mucopolysaccharides in the organs and urine. This may possibly allow more insight into the interrelationship between the gangliosidosis and the mucopolysaccharidosis.

Further detailed clinico-chemical and anatomico-chemical research may yield new facts by means of which the true significance of the undoubtedly important fact that gargoylism is associated with an excess of certain mucopolysaccharides will be better appreciated.

Additional knowledge may deepen insight into certain other affections.

In this connection it should be remembered that gargoylism may be accompanied by cardiovascular sclerosis.

A better understanding of the mechanisms resulting in arteriosclerosis in gargoylism, may further our knowledge of the aetiology of arteriosclerosis in general.

skeletal anomalies he found no ChS-B in the urine. He found an equal proportion of ChS-B to heparitin sulphate to be present in the spleen, kidneys and brain. In the liver, however, heparitin sulphate predominated. The chemical analysis by KARL MEYER of post mortem material from cases VII and XI (the results of the analysis of case XIII are not yet known) yielded the following results:

Patient	Sex	Age	Tissue	Total yield of mucopolysacch. on the basis of defatted dry weight	ChS-B fraction	Heparitin sulphate fraction
G (Case VII)	M	7 years 5 months	Brain	0,84%	40%	30%
			Hepar	1,2 %	5%	90%
K (Case XI)	F	12 years	Brain	2,2 %	85%	15%

III. Comparison of the anomalies in the gangliosides and the acid mucopolysaccharides.

The composition of the three substances which are usually present in excess in gargoylism, i.e. gangliosides, ChS-B and heparitin sulphate is as follows:

	Lipids	Sphingosine	Neuraminic acid	Hexosamine	Hexuronic acid	Sulphate	Acetate	Hexoses	Bound to proteins
Gangliosides	Fatty acids	+	+	Galactosamine	—	—	—	Galactose	+
ChS-B	—	—	—	N-acetyl-galacto-samine	L-Iduronic acid	+	—	+	+
Heparitin sulphate	—	—	—	D-glucosamine	D-glucuronic acid	+	+	+	?

From this survey it appears that both the gangliosides and the mucopolysaccharides contain hexosamine.

On account of this fact BRANTE [279] suggests the following pathogenesis "As to the pathogenesis, it is interesting to note that a connecting link between the gangliosides and the mucopolysaccharides is to be found in their both containing hexosamine in a polysaccharidic structure. The lipids with ganglioside properties are not seen in every case of gargoylism, whereas the above described mucopolysaccharides seem to be. This suggests that the ganglioside deposition might be a consequence, in proper cases, of the mucopolysaccharide surplus, the latter substance perhaps providing raw material for the former. The flooding of the tissues by mucopolysaccharide may, in its turn, be a consequence of some congenital enzyme disturbance as regards the meta-

bolism of the mucopolysaccharide or of some of its components, or as regards the binding of the mucopolysaccharide to protein, etc."

From this it appears that the gangliosidosis is not an essential, or at least not the most essential aspect of the disease.

IV. *Summary and discussion*

According to more recent views, the basic defect in gargoylism is supposed to be a disorder of mucopolysaccharide metabolism[209, 334, 335]. An excess of mucopolysaccharides has been demonstrated in the liver, spleen, meninges, urine[209, 257, 276, 298, 327] and also although to a lesser extent, in the brain tissue of patients with gargoylism[335].

The gangliosidosis, affecting principally the nervous system but also, to a lesser degree other tissues and organs[78, 116, 169, 264, 298], has to be considered as non-obligatory and constitutes in this sense a secondary phenomenon. We suspect the gangliosidosis to be absent in typus E, because here there is no cerebral involvement.

It may be important to know whether or not there are differences between the classical types and typus E as to the chemical nature of mucopolysaccharides in the organs and urine. This may possibly allow more insight into the interrelationship between the gangliosidosis and the mucopolysaccharidosis.

Further detailed clinico-chemical and anatomico-chemical research may yield new facts by means of which the true significance of the undoubtedly important fact that gargoylism is associated with an excess of certain mucopolysaccharides will be better appreciated.

Additional knowledge may deepen insight into certain other affections.

In this connection it should be remembered that gargoylism may be accompanied by cardiovascular sclerosis.

A better understanding of the mechanisms resulting in arteriosclerosis in gargoylism, may further our knowledge of the aetiology of arteriosclerosis in general

skeletal anomalies he found no ChS-B in the urine. He found an equal proportion of ChS-B to heparitin sulphate to be present in the spleen, kidneys and brain. In the liver, however, heparitin sulphate predominated. The chemical analysis by KARL MEYER of post mortem material from cases VII and XI (the results of the analysis of case XIII are not yet known) yielded the following results:

Patient	Sex	Age	Tissue	Total yield of mucopolysacch. on the basis of defatted dry weight	ChS-B fraction	Heparitin sulphate fraction
G (Case VII)	M	7 years 5 months	Brain	0,84%	40%	30%
			Hepar	1,2 %	5%	90%
K (Case XI)	F	12 years	Brain	2,2 %	85%	15%

III. Comparison of the anomalies in the gangliosides and the acid mucopolysaccharides.

The composition of the three substances which are usually present in excess in gargoylism, i.e. gangliosides, ChS-B and heparitin sulphate is as follows

	Lipids	Sphingosine	Neuraminic acid	Hexosamine	Hexuronic acid	Sulphate	Acetate	Hexoses	Bound to proteins
Gangliosides	Fatty acids	+	+	Galactosamine	—	—	—	Galactose	+
ChS-B	—	—	—	N-acetyl-galactosamine	L-Iduronic acid	+	—	+	+
Heparitin sulphate	—	—	—	D-glucosamine	D-glucuronic acid	+	+	+	?

From this survey it appears that both the gangliosides and the mucopolysaccharides contain hexosamine.

On account of this fact BRANTE[209] suggests the following pathogenesis. "As to the pathogenesis, it is interesting to note that a connecting link between the gangliosides and the mucopolysaccharides is to be found in their both containing hexosamine in a polysaccharidic structure. The lipids with ganglioside properties are not seen in every case of gargoylism, whereas the above described mucopolysaccharides seem to be. This suggests that the ganglioside deposition might be a consequence, in proper cases, of the mucopolysaccharide surplus, the latter substance perhaps providing raw material for the former. The flooding of the tissues by mucopolysaccharide may, in its turn, be a consequence of some congenital enzyme disturbance as regards the meta-

lesion consists of swelling of the cytoplasm, usually followed by enlargement. The cytoplasm may have a vacuolar, granular or clear appearance. Generally speaking the extra-cellular lesions are characterized by an abnormal fibrillary structure and swelling of the connective tissue. It is not clear whether the one category is dependent on the other. Certain organs or systems are usually involved, others less frequently. In most cases the reticulo-endothelial system has been found to be affected. It should be mentioned, however, that cases are known, as appears from a publication of GUELI and SEVERI [205], in which typical lesions of the liver parenchym cells are found without involvement of the cells of Kupffer.

It is striking that in one of our cases (Chapt V, report No 1), in which the illness was present in the initial stage, lesions were found in both liver parenchym and Kupffer cells, while in another case (Chapt V, report 2), in a more advanced stage, lesions of the liver parenchyma only appeared to be present.

Neither from the literature nor from our own experience is it clear whether or not the anomalies of the R.E.S precede those outside this system

The pathological processes are progressive. Apart from differences according to the stage of the disease, there are also differences which seem to be irrespective of the stage. Amongst these may be mentioned the absence of neuronal changes in certain cases Changes in the liver cells may not occur; cartilage ossification disturbances may be absent as well as heart, R.E.S, eye anomalies etc. Thus differences are found in the distribution of the pathological lesions, which are dependent neither on the severity nor on the stage of the disease

Approaching the essentials of the disease from the *histochemical* standpoint, one is struck by the difficulty experienced in identifying in many cases the chemical nature of the material(s)s present in the swollen and or enlarged cells Here a distinction should be made between the chemical analysis of the central nervous system and the other organs and tissues

In most cases histo-chemical evidence may be obtained of the presence of an excess of ganglioside-like material in the neurons

The amount of the material in the other organs and tissues, however, does not co-incide in most cases with the degree of cellular enlargement, therefore the products (lipids, glycogen) can only be regarded as accessory More satisfying results are only obtained in those cases in which one has succeeded in demonstrating the presence of mucopolysaccharides In these cases the amount of the substance demonstrated appeared to vary according to the degree of cellular enlargement

The conception of BRANTE namely that, in the extra-neuronal tissues and organs, abnormally strong soluble mucopolysaccharides are stored, is in this connection acceptable.

Other investigators consider the nature of the stored substances to vary according to the type of cell

Chapter VIII

ESSENTIAL FEATURES OF GARGOYLISM

We shall now endeavour to summarize the most essential features of gargoylism by reviewing the following.

a. The clinical data.
b. The pathological and histochemical data.
c. The clinico-anatomical relationship.
d. The biochemical data
e. The genetic data

Ad. a.

The vividness of the clinical picture depends on the stage as well as on the type of the disease. There are more signs in the final stage of the disease Typus E is less rich in clinical signs than the classical type.

The most outstanding clinical feature and one invariably present in all types, is the typical gargoyle habitus.

All other signs, such as the Hurler-face, cardiopathy, hydrocephalus, oligophrenia and mental deterioration are not invariably present

From the literature the impression is gained, that there is no clear correlation between the several possible signs of the disease.

X-Ray evidence of skeletal anomalies can be lacking in cases which otherwise show a classical picture [195, 335] Hydrocephalus was described in patients where neither the liver nor spleen were enlarged [23, 156, 158]

There are also cases in which distinct skeletal anomalies were unaccompanied by hepatosplenomegaly [17, 199]. It should, however, be mentioned that in such patients hepatosplenomegaly may still develop [198] There are cases known without skeletal anomalies but with hepatosplenomegaly [195] The nervous system may remain unaffected, as has been explained in Chapter II From the preceding follows that there are no reasons for assuming that a fixed correlation exists between the various possible signs of the disease

Ad b.

Gargoylism is, in fact, distinguished by intra- and extra-cellular lesions, without a fixed pattern in respect to topographic distribution *The cellular*

bance of the eighth nerve seems to be not *satisfactorily explained. Perhaps* by a minute investigation of the whole vestibular and cochlear apparatus a correlative pathological substratum could be traced.

Apart from these details there is the *important question* whether on pathological examination a correlative or explanatory substratum is to be found for the outstanding *clinical phenomenon*, the typical habitus of gargoylism. There is no generally accepted *opinion about it*. As a rule it has proved to be impossible to show a convincing relationship between the pathological substratum and the abnormal habitus of the gargoyle patient. In cases associated with dwarfism, *disturbances* are often found at the epiphysial lines, yet such clinical and pathological findings may be lacking in cases which exhibit the abnormal habitus.

Neither is there sufficient evidence for assuming a correlation between the abnormal habitus and pathological anomalies of the endocrine system

Ad. d

BRANTE and KARL MEYER showed that a surplus of mucopolysaccharides is present in most organs. This obviously points to a disturbance in the metabolism of the mucopolysaccharides.

Whether this is a primary or a secondary disturbance, *is not yet known with* any certainty Its aetiology is also as yet unknown. Most investigators think it to be due to an enzymopathy, while others consider a possible hormonal defect.

Ad e

The heredity data can be summarized as follows.

The disease can be associated with the anomaly of a single gene, situated in the *X-chromosome*, or with two genes, of which the one is situated in an autosome of the father and the other in *the corresponding gene of the mother. The single gene defect usually* coincides with the absence, the double gene defect usually with the presence of corneal cloudings TURPIN and LAFOURCADE[227] *regard this* as the confirmation of a well known rule that the two dose (homozygous) condition is *more extreme than the one dose (heterozygous)* condition

Summarizing what has been said in ad a, b, c, d, and e, it may be said that the crucial symptom connecting the different *types of* gargoylism is the typical habitus

The varying symptomatology *corresponds* with the varying distribution of the pathological lesions

In the disease *great* significance should be attributed to the disturbed metabolism of the mucopolysaccharides whether this be a primary or secondary characteristic, the cause of this *condition is not* yet known

A striking conditioning factor is *the heredity*. The heterozygous condition seems to be less severe than the homozygous one.

The essentials of the histochemical findings may be summarized as follows: It is generally agreed that in the neurones abnormal quantities of a ganglioside-like material are present.
Regarding the nature of the accumulated material in the extra-neuronal tissues and organs, there is a divergence of opinion:
Some are of the opinion that it consists mainly of mucopolysaccharides; others assume that the chemical nature of the products varies according to the kind of cell in which it is stored.

Ad. c.

In Chapter I a survey is given of what is known, according to the literature, of the correlation between the clinical findings and the pathological processes. These findings will not be repeated here. We shall restrict ourselves to the following additions based on our own investigations:

1. What pathological substratum is responsible for the corneal cloudings? The general opinion expressed in the literature is that these are brought about by the presence of gargoyle cells in Bowman's membrane. However, we found in the literature several cases with corneal cloudings without gargoyle cells in Bowman's membrane and other cases in which the topography of the cells does not tally with the distribution of the cloudings.
In our own material, one patient (Chapt. IV, case XIII) with corneal cloudings, proved (Chapt. V first report) to have a normal membrane of Bowman In this case however a pronounced oedema of the substantia propria was observed
From this it appears that there is not always relationship between corneal cloudings and the presence of gargoyle cells.
2. In the literature deafness or diminished hearing is assumed to be a frequent symptom.
In Chapter III we stated that on account of psychical disturbances it is difficult in most patients, to establish exactly whether or not the hearing is impaired.
There is also little known in the literature regarding the vestibular function of the patients examined.
Caloric stimulation of the labyrinth did not produce a single vestibular reaction in many of the patients described in Chapter IV while in most of the remaining patients the impression was gained that irritability was subnormal. All these patients, however reacted to sound stimuli. From this it may be concluded that in several patients there was a *dissociated* function disturbance of the eighth nerve. In one of these (Chapter IV, Case VII), the pathological findings (Chapter V, fourth report) were in agreement with those of RICCI and ANCETTI [271], viz., degenerative or thesaurismotic changes were found in the ganglion cells, as well in those of the vestibular as in those of the cochlear ganglion The changes in the vestibular ganglion were not more marked than in the cochlear ganglion. The dissociated function-distur-

bance of the eighth nerve seems to be not satisfactorily explained. Perhaps by a minute investigation of the whole vestibular and cochlear apparatus a correlative pathological substratum could be traced.

Apart from these details there is the important question whether on pathological examination a correlative or explanatory substratum is to be found for the outstanding clinical phenomenon. the typical habitus of gargoylism. There is no generally accepted opinion about it. As a rule it has proved to be impossible to show a convincing relationship between the pathological substratum and the abnormal habitus of the gargoyle patient. In cases associated with dwarfism, disturbances are often found at the epiphysial lines, yet such clinical and pathological findings may be lacking in cases which exhibit the abnormal habitus

Neither is there sufficient evidence for assuming a correlation between the abnormal habitus and pathological anomalies of the endocrine system.

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The disease can be associated with the anomaly of a single gene, situated in the X-chromosome, or with two genes, of which the one is situated in an autosome of the father and the other in the corresponding gene of the mother. The single gene defect usually coincides with the absence, the double gene defect usually with the presence of corneal cloudings TURPIN and LAFOURCADE[227] regard this as the confirmation of a well known rule that the two dose (homozygous) condition is more extreme than the one dose (heterozygous) condition

Summarizing what has been said in ad. a, b, c, d, and e, it may be said that the crucial symptom connecting the different types of gargoylism is the typical habitus

The varying symptomatology corresponds with the varying distribution of the pathological lesions

In the disease great significance should be attributed to the disturbed metabolism of the mucopolysaccharides whether this be a primary or secondary characteristic, the cause of this condition is not yet known

A striking conditioning factor is the heredity. The heterozygous condition seems to be less severe than the homozygous one

Chapter IX

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

A. Diagnosis:

The diagnostic criteria for the different types of gargoylism may be summarized as follows.

Type	Classic Type	Typus E	Abortive cases Cases with the disease in its initial stage
Gargoyl habitus	+	+	+
Hurler's face	+	+	±
Hepatomegaly	+	+	±
Typical X-Ray findings	+	+	±
Sella anomalies	±	±	±
Contractures	+	+	±
Typical neuropsychiatric disturbances	+	—	±
Cardiovascular sclerosis Splenomegaly Corneal cloudings Teeth anomalies Macroglossia Nail anomalies Hair anomalies Herniae Disturbance in labyrinth function Reilly's anomaly	±	±	±

\+ Present
— Absent
± Optional

The alpha-2 globulin fraction of the blood is commonly increased. The determination of the nature and amount of mucopolysaccharides excreted in the urine is important for diagnostic reasons However the determination of this parameter is not yet possible in most laboratories on account of the technical difficulties involved.

Up to the present a simple and reliable method of demonstrating abnormal quantities of mucopolysaccharides in the urine is not available.

B *Differential diagnosis:*

On account of the varied symptomatology there are points of contacts with many other diseases

As such mention should be made of all conditions accompanied by:

1. Hydrocephalus
2. Hepatosplenomegaly.
3. Cardiovascular sclerosis or congenital cardiac malformation.
4. Neurolipidosis, whether accompanied by reticulosis or not
5. Enchondral dysostosis
6. Corneal cloudings
7. Optic atrophy.
8. Sella enlargement.
9. Spastic diplegia
10. Infantile endocrine disturbances.
11. Ligamentary anomalies and joint affections.
12. Inborn errors of metabolism
13. Oligophreny, accompanied or not by dementia
14. Dwarfism
15. Leucocytic granulation anomalies

Ad 1

Pathological conditions in early youth which are accompanied by hydrocephalus include hydrocephalus communicans as disease sui generis, toxoplasmosis hominis, obstructive-hydrocephalus as a result of meningitis or meningoencephalitis, traumatic hydrocephalus, hydrocephalus as the result of cysternitis chronica productiva, hydrocephalus as the result of a cerebral tumour with obstruction of the aquaeduct, intra-ventricular tumours of the third ventricle with occlusion of the foramina of Monro

Ad 2

Hepatosplenomegaly in early youth is seen in cases of congenital syphilis, glycogen-storage disease, definite storage diseases, such as the disease of Niemann-Pick, Gaucher's disease, chronic infectious diseases, such as tuberculosis, malaria, certain benign and malignant reticuloses, cirrhosis of the liver, amyloidosis, blood diseases such as chronic leukaemiae and others

Ad 3

Cardiovascular anomalies are found in youth, in, for example, progeria, periarteritis nodosa and congenital heart disease

Ad. 4.

Examples include: Tay-Sachs's, Niemann-Pick's and Gaucher's diseases

Ad. 5.

The most obvious example is the disease of MORQUIO[24]; also may be mentioned further cystinosis[126] and the disease of ELLIS-van CREVELD[56].

Ad. 6.

Corneal cloudings have been described in a o angiokeratoma corporis diffusum Fabry[125].

A detailed differential diagnosis is described by GASTEIGER and LIEBENAM[38].

Ad. 7.

Optic atrophy is seen a.o in oxycephaly; scaphocephaly; Leber's disease; arachnitis chiasmatis, diffuse sclerosis, amaurotic idiocy; disease of Lawrence-Moon-Biedl.

Ad. 8

Sella enlargement is found in intra-sellar tumours; suprasellar tumours; hydrocephalus; some cases of cretinism, a.o.

Ad. 9.

Diplegia spastica infantilis is seen in several neurological affections in youth, as manifestation of the complicated syndrome of Little. One should be extremely cautious in attributing such like symptoms to anoxia as a result of an abnormal course of birth.

Ad. 10.

The differential diagnosis from cretinism may be particularly difficult.

Ad. 11.

Amongst these may a o. be included arthrogryposis and Marfan's disease[274].

Ad. 12.

As examples may be mentioned Folling's disease, galactosaemia, cysteinurea a o.[330].

Ad. 13.

These include a o mongolism, the disease of Tay-Sachs, phenylketonuria and cretinism.

Ad. 14.

Primary dwarfism should be distinguished from the secondary form Gargoylism must be differentiated here from the disease of MORQUIO, the disease of ELLIS-van CREVELD and cystinosis

As examples of other forms of secondary dwarfism may be mentioned cerebral, hypophyseal, thyrogenic, gonadal, adrenal and renal dwarfism Further it is seen in rickets, cystic fibrosis of the pancreas; infectious processes,

such as congenital syphilis, tuberculosis and toxoplasmosis; and in many affections of unknown or little understood aetiology.

Ad 15

Hereditary anomalies of the white blood cells are described a o. by JORDANS [313]. It is important to note here that in juvenile amaurotic idiocy vacuolar and granular anomalies have been described resembling those found in gargoylism [314].

MORQUIO'S DISEASE

As is stated in Chapter II the absence of storage phenomena in Morquio's disease is accepted by most authors as important in the differential diagnosis from gargoylism As long as the contrary view has not been convincingly proved, this criterion should be maintained

As stated in Chapt. II and VIII, there are reasons for not considering corneal cloudings as evidence of accumulation Accordingly, it seems incorrect to change the diagnosis in an otherwise clear case of Morquio's disease to one of gargoylism, as soon as corneal cloudings appear. Looked at from this point of view, the "Spat-Hurler" type of ULLRICH [11] should constitute a form of Morquio's disease.

What is more reliable than the presence or not of storage phenomena in Morquio's disease, is the difference in general appearance in the two diseases for, as in gargoyle patients there is also a similarity in appearance in Morquio-patients

It is not easy to define precisely this differences in general appearance.

In general it may be said that in gargoylism sthenic features predominate, whereas Morquio-patients give a less sthenic impression.

X-Ray findings cannot adequately differentiate between those two forms However it may be mentioned that in Morquio's disease the Hurler-face is absent, as also the anomaly of Reilly and possibly also the increase of the alpha 2 globulin fraction in the blood serum, perhaps also the abnormal quantity and quality of mucopolysaccharides in the urine is absent

Morquio's disease is further characterized by ligamentary hyperlaxity as opposed to the hypolaxity in gargoylism

Morquio's disease, is, like gargoylism, characterized by the recessive-autosomal or the recessive X-chromosomal heredity, but in addition this disease may also be the result of a dominant inheritance [90] Life expectancy in Morquio's disease is favourable, in this way differing from the frequently bad prognosis in cases of gargoylism



Fig. 66.
Case XIX, Boy S, age 6 years.

CASE XIX

BOY S· (Fig. 66) *

CASE HISTORY.

Patient is the first of two children.
Mp and m^2 are sisters, sm and m^2 are undersized, fm is thought to be suffering from disseminated sclerosis
At the age of one year the patient underwent a double-sided osteotomy for knock-knees.

EXAMINATION (at 6 years)

Length 92 cms (—22,3 cms), weight 15,3 kg (—4,6 kg), largest skull circumference 52 cms (—0,7 cms), skull length width 17 14 cms
The head presents no abnormalities, the facial expression is asthenic.
Further inspection reveals. a short broad neck, marked kyphoscoliosis at the level of the thoracolumbar junction, a broad thorax with pigeon-chest,

* We thank colleague B Bockwinkel that he gave us the opportunity to examine this patient

genua valga and flat feet. The back is very hairy. The musculature is poorly developed

The hands and fingers are short and broad. The little fingers are radially curved. There is a marked hyperlaxity of the ligaments of the wrist, hand and fingerjoints (concertina phenomenon).

The movements in the elbows, shoulder and knee joints are limited.

On slit-lamp examination no corneal cloudings are seen. The fundi oculi are normal Hearing is normal Vestibular stimulation results in normal reactions.

Cardio-vascular examination reveals a murmur over all ostia, most pronounced over the aorta The liver is just palpable.

On neuropsychiatric examination no abnormalities are found, apart from immature asthenic psychomotility.



Fig 67
Hefty clavicles, especially the sternal part
Narrowed ends of lower ribs



Fig 68
Generalized platyspondylia
Fishhookshape of L 1 and 2
Tongue-like protrusions of the vertebral bodies
Backward displacement of L 2 and 3



Fig. 69.
Broad and short metacarpals and phalanges.
Coarse trabeculation
Pseudoepiphysis at metacarpal I.
Pointed proximal ends of metacarpals

Psychological tests show an I.Q of 96 resp. 119 (Stanfort-Binet, resp Pintner-Cunningham).
Electroencephalographic examination yielded a somewhat irregular tracing because alpha-rhythm is interspersed with theta waves Further a marked reaction to hyperventilation is seen.
The E.E G. is considered to be without clear abnormalities.

X-Ray findings:

Skull· No anomalies
Thorax (Fig. 67). Sturdy clavicles, specially the sternal portion The ends of the lower ribs are narrowed.
Vertebral column (Fig. 68): Generalized platyspondylia Tongue-like processes project from the anterior surface of most of the vertebral bodies Backward displacement of L 2 and L 3. Fish-hook shape of L 1 and 2. Microspondylia of L 2. Kyphoscoliosis at the level of the thoraco-lumbar junction.
Pelvis. High and small in shape. Coxae valgae et magnae.
Hands (Fig. 69). Broad, short metacarpals and phalanges with coarse diaphysiary trabeculation, running pointedly from the proximal ends of some of the metacarpals. Pseudoepiphysis at metacarpal I. Cone-shaped phalanges. There are six carpal centres of ossification visible

Laboratory findings:

Blood-serum was normal in respect to the following determinations calcium (10,6 mg %), phosphorus (3,6 %), cholesterol (240 mg %), acid phosphatasis (2,5 KA U), alkaline phosphatasis (9 KA U) Protein spectrum of the

blood-serum is normal regarding the following values. calcium (10,6 mg %), phosphorus (3,6 %), cholesterol (240 mg %), acid phosphatasis (2,5 KA U), alkaline phosphatasis (9 KA U) Protein spectrum of the blood serum determined by means of paper-electrophoresis: albumin: 66,4 %, alpha 1 globulin 1,4%; alpha 2 globulin 8,6%, beta globulin 6 1%; gamma globulin 17,5% The routine blood and urine examination is normal. Reilly's anomaly is not present

Diagnosis Morquio's disease.

The diagnosis is based on the following considerations:

1 The typical Morquio-habitus
2 The absence of the Hurler-face.
3 Absence of storage phenomena.
4. Generalized platyspondylia.
5 Ligamentary hypolaxity.

Ad 3

Apart from the absence of phenomena indicating neurolipidosis, the underweight also suggests an absence of storage.

The liver, however, is just palpable. Should this be attributed to displacement by the thoracical deformity?

WIEDEMANN is of opinion that Morquio's disease may be accompanied by liver enlargement or other storage phenomena.

Liver biopsy should in our opinion be the procedure of choice in the settling of this question

SUMMARY

The term GARGOYLISM represents a syndrome of which there are a number of types.

Typus E, distinguished from the classical type by C. de LANGE and WOLTRING, is characterized by an absence of neurolipidosis and the clinical symptoms associated with this condition. Clinically typus E seems to carry a more favourable life expectancy and neurological complications and mental deterioration are not detectable. Since in both the classical type and in typus E *deafness and sella anomalies may occur, it appears that the primary cause* of these signs should not be sought for in the neurolipidosis The classical type is accompanied by an excess of mucopolysaccharides and gangliosides, but in typus E, on the other hand, the latter is probably absent

There is much variety in the clinical picture, the most prominent feature being the typical gargoyle habitus; all other signs are facultative

A clinical investigation of eighteen patients resulted in the discovery of a number of signs which have not, to the best of our knowledge, been described in the literature, these are namely, leukonychia, a dissociated functional disturbance of the eighth nerve, and an association of a small degree of cranial enlargement with mesocephaly.

The neuropsychiatric features may be summarized as follows.

1. A progressive deterioration process preceded by oligophrenia
2. A slowly progressive neurological condition, finally resulting in a spastic tetraparesis or tetraplegia and cortical, subcortical, striate and brainstem lesions.
3. Hydrocephalus in the great majority of cases.

There was much variation in the neuropsychiatric picture, for example apathy, as well as erethic patterns of behaviour were found Similarly both motor inertia and restlessness were to be observed.

A rather frequently encountered phenomenon was an increased oculopalpebral reflex with extension of its reflexogenic zone

Primitive oral libidinous behaviour characteristics were *often present in the* later stages of the disease.

The part played by the reticulo-endothelial system in the disease as a whole is not easily understood. Anomalies of the RES were present in most cases.

Clinico-pathological comparisons brought the following facts to light

a Corneal cloudings are not necessarily evidence of the presence of gargoyle cells in the cornea.

b In our material a correlation was found between the degree of cranial enlargement and ventricular dilation.

From the biochemical standpoint the disease is associated with either a primary or secondary metabolic disturbance of mucopolysaccharides, the cause of which is unknown

In this publication a sex-linked case of gargoylism is presented which was complicated by corneal cloudings, a phenomenon believed previously to be invariably lacking in these cases; it is concluded that as a rule the homozygous condition is more extreme than the heterozygous one, owing to the fact that the former is characterized by a higher incidence of cornea cloudings and a poorer life expectancy It is not considered proven that the homozygous condition is accompanied by a higher incidence of hearing defects.

The disease of Morquio, although in many respects an allied disorder, has its own typcial characteristics and therefore should be distinguished from gargoylism

ERRATUM

On page 132 lines 17 and 18,

read an association of a small degree of cranial enlargement with brachycephaly and a high degree with mesocephaly

On page 133 lines 16 and 17,

read It is not considered proven that the heterozygous condition is accompanied by a higher incidence of hearing defects

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Typus E, distinguished from the classical type by C de LANGE and WOLTRING, is characterized by an absence of neurolipidosis and the clinical symptoms associated with this condition Clinically typus E seems to carry a more favourable life expectancy and neurological complications and mental deterioration are not detectable. Since in both the classical type and in typus E deafness and sella anomalies may occur, it appears that the primary cause *of these signs should not be sought for in the neurolipidosis.* The classical type is accompanied by an excess of mucopolysaccharides and gangliosides, [illegible] the other hand, the latter is probably absent.

Primitive oral libidinous behaviour

later stages of the disease.

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LIST OF PUBLICATIONS

(in chronological order)

1 *Berkhan, O.* Zwei Falle von Skaphokephalie
Archiv fur Anthropologie. 34: 8-11 1907.

2. *Hunter Ch.* A Rare Disease in Two Brothers
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